



# Endocrinology

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# Endocrinology

## *The Bulletin of the* *Association for the Study of* Internal Secretions

January-February, 1928

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### STUDIES OF THE ENDOCRINE GLANDS. I. A GENERAL METHOD FOR THE DIAGNOSIS OF ABNORMAL FUNCTION

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From the Evans Memorial  
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This paper is the first of a series summarizing the results of a study on the diagnosis of endocrine diseases by objective methods. The work was begun in 1912 and in its course nearly 3,000 individuals have been carefully studied by a large group of clinicians and laboratory workers.

During the past few years several brief papers have appeared (1) presenting certain preliminary statements on the results of these studies. These have been supplemented by the reports of several clinical investigations based upon the method (2). With the completion of a series of 1,000 cases in which this procedure has been applied,\* it has seemed desirable to present the facts thus far elicited with such conclusions as they may be felt to warrant. The present paper, as the title implies, deals with the general technique. Subsequent papers will present the details of the characteristic pictures of each of the

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\* Since beginning the compilation of the data here presented, over 2000 additional cases have been studied. The findings in the second group confirm and amplify, in a most gratifying manner, the conclusions drawn from the first.

several established endocrine entities. Finally, special treatment will be accorded those conditions which simulate endocrine disease and are frequently erroneously ascribed to it, but which can be shown by objective study to result from disease states not associated with the ductless glands.

The science of endocrinology, if so ambitious a designation be warranted, constitutes one of the newer chapters in medical history, and one that is still in the writing. True, the general concept of an internal secretory activity was first offered many centuries ago, but in this earlier form it derived solely from uncontrolled speculation and not from observation and experiment. First in the 19th century did certain definite, well-described clinical entities come into being in which an endocrine etiology was recognized by the individual authors whose names these syndromes bear, and toward the end of this period active glandular extracts were prepared and therapeutically applied. Finally, at the very beginning of the present century, Abel and others isolated the first active principle in a pure state.

These investigations, of which this paper is the first formal statement of results, are the expression of an effort to establish a series of objective criteria both for the general identification of disturbed endocrine function, and particularly for the determination of the individual gland involved. The field of so-called vital function testing has offered rich possibilities both by standardizing tests already described and by formulating new procedures when such were needed.

In the main, vital function tests have been designed to indicate an individual departure from the normal and have sought a marked degree of specificity. With the highly complex control of individual bodily functions, it has followed naturally that the reporting of each new test has been a signal for the recording of sweeping exceptions of both a positive and negative character. By questioning the specific character of the test its results have lost authority, and this in turn has frequently discouraged further study and application. Such an outcome is unfortunate and unwarranted. The level of any body function is certainly controlled by a large number of interrelated agencies which are mutually dependent and highly sensitive to changes in any one of them. The disturbance of any one equilibrium produces

changes in the balance of a number of other related control factors and may produce end results of a really significant character. As a vital function test can, at best, only record end results, a lack of complete specificity is confidently to be predicted. Even the highly differentiated tests in the field of serology fail to fulfill their purpose completely.

From another standpoint, however, this very multiplicity of control factors offers the largest element of value. The selection of a series of function tests gives not a single criterion of a single disturbed function, but a series of interrelated criteria in each of which several functional activities are involved. Thus while several factors influence the magnitude and direction of the result of each observation, it seems highly improbable that all of a series of widely divergent tests should be uniformly affected both in quality and amount by each of the several agents involved. The accuracy of this assumption has been amply verified in the series of cases reported in these papers. In passing, the writer wishes to state that no novelty is claimed for the majority of the tests, as such. It is chiefly in the angle of approach that the present method differs from others.

A point that cannot be over emphasized is the necessity for quantitative measurements. Differences as observed in many instances must be of degree and not of kind. Only the most exact methods available are suitable for this purpose and these should be as rigorously quantitative as possible.

The investigation has naturally divided itself into three phases. In the beginning, groups of apparently normal individuals were subjected to a long series of tests and observations under carefully controlled conditions, and the individual level of performance exactly recorded. Tests were retained or discarded as they served or failed to define standards of normality within reasonable limits of variation.

The second phase of the study called for the application of the same series of measurements to individuals in whom there existed clear-cut involvement of single glands. To this group belong male and female castrates and thyroid and pituitary patients after ablation operations. In addition, a few progressing cases of exophthalmic goiter and of acromegaly were studied with just recognition of the uncertainty of their true etiology. The impossibility of establishing adrenal failure in man by sur-

gical means limited the inclusion of this gland to the rare case of Addison's disease, in which the probable underlying pathology possibly later could be established by necropsy. The very small number of such cases which have been studied prevents that clear-cut definition which the other principal glands possess. The application of the tests to this entire group indicated both the directions and magnitudes of departure from the several base lines, and also established certain norms which were equally significant for the purposes of differential diagnosis.

These standards of performance indicate trends in functional change, the absolute magnitudes being conditioned by the severity of the disease and such intrinsic variables as age, sex, and similar biological factors. The influence of these latter makes it essential, where possible, to express results in relative terms, rather than those of the absolute data from which the relationships derive. For example, basal rates are profoundly influenced by both age and sex, as well as by such other standard measurements (height, area, etc.) as have been selected for correlation purposes. In like manner, the galactose tolerance of the normal female varies throughout the life span, apparently being regulated by the level of sexual activity; the normal male, on the other hand, presents an unvarying level from birth to death. With standards which are themselves variable through biological change, relative values are necessary for any basis of comparison.

In the collation of data certain other factors must receive due and constant consideration. For purposes of clarity, certain terms must be defined in order that in later use they may possess a constant meaning.

The term "hypofunction" is applied to that condition in which all of the clinical and laboratory findings indicate a lowered functional level—the extreme picture of which is produced by complete ablation of the gland—in other words, a state of demonstrable diminution or lack of internal secretory activity.

"Hyperfunction" is used to indicate a condition in which all measurable function levels are of opposite sign to those produced by ablation.

"Dysfunctional" states are those in which evidences of hyper- and hypo-activity are simultaneously observed. Such conditions arise, for example, when endocrine organs initially hyper-

active are undergoing a functional involution to an ultimate hypoactive state. Years ago Cushing (3) called attention to such involutions in acromegaly, and the writer and his associates have frequently observed analogous conditions in thyroid disease. When such involutions occur, all the functions influenced by the gland at fault are not affected at the same rate of speed, and a variety of intermediate pictures is seen, depending upon the degree of the involution at the time of observation.

A second factor in the production of dysfunction lies in the plurality of certain of the endocrine structures. The adrenal, the adult ovary, and the pituitary, all embody certainly two functionally independent tissues, and with the last named yet other possibilities exist. Further, the single gland may produce more than one active principle as the result of its endocrine activities. These several variables naturally can produce a number of intermediate dysfunctional states. With the two extreme functional pictures properly defined, however, these intermediate conditions may be capable of at least a partial analysis.

The third and last phase of the investigation has been the study of the level of function of the individual case. After the careful elimination of all non-endocrine disease conditions which might produce the observed deviations from the norm, the data have been interpreted to define a tentative endocrine diagnosis. Finally, the indicated corrective measures have been applied, under careful clinical control and with repeated laboratory tests, to that gland which has been shown probably to be at fault.

Certain points in the foregoing require brief exposition for the sake of emphasis.

First, no single test can be regarded as significant unless it be checked and controlled by a number of other independent observations. For example, the diagnosis of thyroid disease on the basis of the basal metabolic rate alone is wholly unwarranted. Such a practice could lead to the performance of a thyroidectomy in a case of leukaemia, and certainly has caused the administration of vast quantities of thyroid preparations to individuals with normal thyroid glands.

Second, no single finding suggestive of an endocrine disease should be adduced to support such a diagnosis until all possible non-endocrine causes of the phenomenon have been ruled out by



observation and test. For example, a slight eosinophilia is found in pituitary disease, but should be regarded as signifying such a condition only after the elimination of acute infections, protein sensitivity, skin eruptions, and intestinal parasites—to name but a few among the many. Over-enthusiasm in the interpretation of tests to support an endocrine diagnosis may well lead to the failure to recognize the true underlying cause of the patient's disability.

Third, in the study of each case, careful clinical observation is as important as are laboratory tests. The latter furnish a basis of tested fact for the interpretation of the subjective evidences of the former. But equally, medical history and physical examination offer data which may definitely establish the diagnosis, the laboratory findings serving chiefly as confirmatory supporting evidence. Both are essential, the one complementing and supplementing the other, with the diagnosis resulting from a judicious combination of the factors of each.

One other matter may be briefly considered. In the following pages results will be given from cases exhibiting disease of the pituitary, the thyroids, the gonads, and the adrenals. The pancreas has been omitted since the determination of diabetes—and the writer is in accord with Allen (4) in the limitation of this term to the syndrome caused by failure of the islands of Langerhans—does not usually require so elaborate a procedure as that to be described. The parathyroids have also been omitted because but little is known concerning the disease picture produced by disturbance of their function. On the one hand, several different causes may produce a low blood calcium, and on the other, the correlation of certain disease states with parathyroid inadequacy rests solely on unchecked speculation. In a recent treatise on these glands, Vines (5) reviews a series of conditions said by some to be benefited by parathyroid therapy that would place this product in successful competition with any of the six best sellers of proprietary origin.

A few glandular structures, such as the pineal, thymus, and spleen, are to be regarded as on the borderline, their place in the endocrine family by no means firmly established. Yet other tissues seemingly enjoy their endocrine status through the brevet conferred upon them by the manufacturers of pharmaceutical preparations.

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The pluriglandular group, discussed in the later pages, is made up almost without exception of cases in which surgical intervention in one endocrine gland is superimposed upon functional aberration in another. In a series of nearly 3,000 cases the writer has seen but two or three in which there has been apparently a coexistent primary disturbance in more than one endocrine gland. With this truly insignificant proportion, common sense would ascribe the failure to define a single primary focus rather to the lack of knowledge of the observer than to the existence of the conventional pluriglandular syndrome. This statement is not intended to deny the possible existence of a true pluriglandular state, but only to emphasize the essential rarity of such a condition. True, the endocrine glands are among the powerful regulators of the general body metabolism, and failure of any one of them engenders functional derangement in other endocrine and non-endocrine tissues alike. This relationship is one of sequence and does not determine a pluriglandular syndrome in the conventional sense. Further, treatment solely of the primary focus—and if the secondary changes be in a reversible phase—if successful, corrects these latter as a result of normalizing the gland initially at fault. A pertinent illustration is the amenorrhoea of pituitary or thyroid origin.

In the latter discussion, the pituitary and thyroid cases are classified as “hyper-”, “hypo-”, and “dys-functional,” in accordance with the definitions discussed above. The gonad cases are all classed as “hypo-functional,” and to this exception may be taken. The writer has never seen a case of hyper-gonadism. *i. e.*, one presenting a picture the opposite of that produced by castration. The diagnosis of hypergonadism in cases referred for study is usually found to be based upon a record of a libido in excess of the observer’s concept of the normal. Failing one terminal phase, an intermediate dysfunctional state is hard to define. For this reason, the writer has adopted the simplified classification, recognizing the limitation of its use. For similar reasons, the adrenal cases are also grouped in the single category. There is perhaps even less warrant for this, but if it errs, it is on the side of conservatism.

As the work was first outlined and undertaken, the subjects were admitted to the hospital for a period of seven days, and were thus under control for the duration of the study. The re-

sults of certain tests presuppose an adequate nutritional level, and consequently a diet was outlined to meet this requirement.

As these investigations were not intended to be exact metabolism studies in the sense, for example, of a nitrogen balance measurement, every effort was made to render the diet as varied and palatable as possible. As no exact analysis of the food intake was required, values as computed from Locke's compilation (6) were sufficiently accurate for the purpose. As the writer has elsewhere emphasized (7), such elastic regulation of the diet is of importance in experiments of any duration. The average individual, indifferent alike to the urge of pure science and the enthusiasm of the dietary propagandist, is influenced unfavorably, both directly and indirectly, by the continuance of an unvaried and potentially unpalatable diet. Diets were designed to give at least 6 grams of carbohydrate, 1.5 grams of protein, and a gross energy content of 45 calories per kilogram of body weight. Patients have been permitted to exercise a large degree of freedom in relation to their diet, and in the later studies it has been found necessary only to insure a protein intake above a maintenance level and a carbohydrate allowance sufficient to prevent depletion of the glycogen reserve. In general, the ordinary hospital fare, as outlined by a competent dietitian, has been found entirely satisfactory. In isolated cases patients are under special dietary regimen at the time of reference, and this is continued during the hospital stay. For those preferring it, lunch is served at noon and the heavy meal at night. Regulation is secured in the amounts served, not in limitation of the variety.

In connection with the liberal dietary provision, every effort has been made to have the patient's hospital stay depart as little as possible from a normal regimen. Schedules, to be discussed later, are drawn to allow for free hours, and patients are encouraged to go out, see friends, and indulge in reasonable recreation, including theater attendance and other evening diversions. This serves the purpose of minimizing the irksomeness of an enforced hospital stay and, most importantly, produces a state of mind which makes for a maximum of co-operation. In the writer's opinion, this provision should be stressed, as certain of the tests are undoubtedly influenced by the patient's mental state. The more nearly the patients' lives in the hospital compare with

their daily habit, so more nearly are the conditions reproduced under which they have experienced their individual symptoms.

As was intimated above, to conserve the patients' time and yet to permit thorough study, a definite schedule has been drawn up which outlines the sequence of certain basic routine procedures and allows opportunity for the inclusion of a wide variety of special examinations. These latter are selected on the basis of the suggestions developed in the routine examination. Patients are received only on Saturday afternoons, and under ordinary circumstances are discharged one week later. Where certain procedures are found to be necessary which are time consuming and do not permit the simultaneous performance of the routine tests [gastro-intestinal x-ray series, Graham test, duodenal function (McClure), and similar observations], the patient is held over for such additional days as are required. Routine tests are performed in duplicate or even repeatedly, if first results are uncertain. The general form is shown in Table I. It is understood that selections are made from the special examination group to conform with the needs of the individual patient.

TABLE I

GENERAL SCHEDULE ("Long Form")

ROUTINE PROGRAM	SPECIAL EXAMINATIONS
<i>First Day (Sunday)</i> A. M.	
7:00 Start collection Urine I.	
7:30 Blood I. Complete Morphology.	
7:35 Breakfast. Diet begins (1).	
9:30 Physical Examination.	
P.M.	
History.	
<i>Second Day</i> A. M.	
7:00 Complete Urine I.	Sputum Collection.
10:00 Phenol Sulphone Phthalein.	Special Liver Function.
	Electrocardiogram.
	Endermal Tests.
P. M.	
12:30 Lunch. Salol I.	Psychometric Examin't'ns
2:30 Adrenalin Mydriasis.	Psychiatric "
4:00 Alveolar CO <sub>2</sub> I. Blood Pressure.	Neurological "
	X-Ray (general).

*Third Day* A. M.

7:00 Start collection Urine II.

8:00 Basal Metabolism.

Vital Capacity.

Alveolar CO<sub>2</sub> II.

9:30 Breakfast.

P. M.

Respiratory Quotient.

Faeces Collection (2).

Physical Measurements.

Surgical Examinations.

Pelvic “

Otological “

Neuro-Otological Exams.

Ophthalmological “

Audiogram.

Photographs.

X-Ray (general).

*Fourth Day* A. M.

7:00 Complete Urine II.

8:00 Basal Metabolism.

Spirometer Measurements.

9:30 Breakfast.

10:00 Phenol Sulphone Phtha-

12:00 lein.

P. M.

Repeat second day.

Gastric Function.

Pneumograph Records.

Electrocardiogram.

Polygraph Record.

Cystoscopic Examinations.

Cardiac “

Chest “

X-Ray Pyelograms.

Neurological (Electrical)  
Examination.

Audiogram.

*Fifth Day* A. M.

5:00 Start Collection Urine

G-1.

6:45 Blood II (3).

7:00 Complete Urine G-1,

Start G-2.

Test Meal of Galactose I

(20 grams).

(+15 gms. Urea in 200 cc.

H<sub>2</sub>O) (4).

9:00 (5) Complete Urine G-2.

Start G-3.

11:00 (5) Complete Urine G-3.

Start G-4 (4).

Breakfast.

P. M.

1:00 (Complete Urine G-4)

Dental Examinations.

Laryngological “

Ophthalmological “

Certain special Examina-  
tions of morning of 4th  
day.

6:45 Blood III for Blood Sugar

9:00 Curve.

(Stool) (2).

Lumbar Puncture.

Special Examinations.

(Psychological.)

(Psychiatric.)

*Sixth Day* A. M.

5:00 Start Collection Urine

G-1a.

7:00 Complete Urine G-1a.

Start G-2a.

Test Meal of 5th day (7)

± 10 or 20 gms.

Galactose (10-20% solu-  
tion).

9:00 (5) Complete Urine G-2a.

Start G-3a.

11:00 (5) Complete Urine G-3a.

Breakfast.

6:45 Blood Chemistry II.

Urea Index (R. W.).

Stool (2).

Chest Examination.

P. M.

Lumbar Puncture.  
Special Renal Tests.

*Seventh Day*

A. M.

Repeat 6th Day Schedule, changing Galactose Test Meal of 6th day (7)  $\pm 5$  to 20 gms. Collecting Urines G-1b, 2b, 3b.

11:00 Test ends  
or

Omit 3rd Galactose Test and start Gastro-duodenal Function Test (McClure).

Or, Gastro-Intestinal X-Ray Series (6).

Or Graham Test (6).

Or Start Mosenthal Diet for Kidney Function.

P. M.

Repeat Phenol, Sulphone, Phthalein.

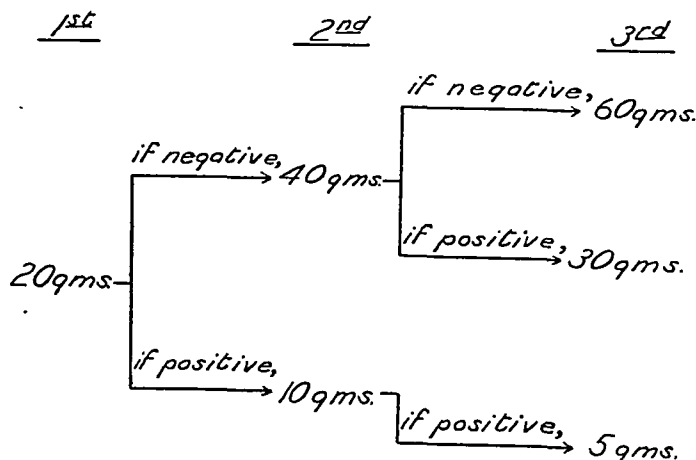
*Eighth Day*

A. M.

Complete Galactose III or Gastro-Intestinal X-Ray Series (6), or Graham Test (6), or perform Mosenthal Test.

- (1) Unless otherwise noted, meals are served at 7:30 a. m. and 12:30 and 5:30 p. m., respectively.
- (2) If for blood examination, postponed and diet suitably modified before collection.
- (3) Diet of preceding day is creatinin free.
- (4) Included only when kidney function is desired.
- (5) Patient remains in bed until 9:00 or better 11:00 a. m.
- (6) If both Graham and G. I. Series desired, the former is done first and patient remains in hospital until completion of second.
- (7) Galactose Chart, q. v.

*Days of Test*



The scope of certain of the examinations listed above is given in the next table.

TABLE I-a

<i>Urine</i> —I and II	G-1, 2, 3, 4; G-1a, 1b, 1c; 2a, 2b, 2c	
Complete Routine	Sugar	Sugar
Nitrogen Partition	Urea	
Microscopy of Sediment		
"Urobilinogen"		
Special test as indicated		
<i>Blood</i> —I	II	III
Morphology	Morphology	Sugar
	Serology	Urea
	Chemistry	
	N. P. N.	
	Urea	
	Uric Acid	
	Creatinin	
	Sugar	
	Special tests as indicated	

While the method of study outlined above gives a large amount of correlated information, it is time consuming, and moreover, the enforced hospital stay is a definitely limiting condition. Further, the underlying etiology in a number of cases can be determined with a much less elaborate and detailed examination. To meet this need, an abridged schedule has been outlined, embodying certain essential features of the longer study, and this "short form" has proven most helpful in the resolution of diagnoses. The essential features are given in the next table.

TABLE II  
Abridged Schedule ("Short Form")

The patient reports at the hospital at 8 a. m. (or somewhat earlier) in a fasting state, and bringing the full 24-hour collection of the urine completed on that morning. After a suitable period of rest, the following schedule is carried out:

8:00 A. M. Basal Metabolism (first measurement at 8:30 or later).  
Vital Capacity Measurements.  
Alveolar Carbon Dioxide.



- 9:00 A. M. Injection of Phenolsulphonephthalein.  
Physical Examination.  
Medical History.
- 10:00 A. M. First P-S-P Collection.  
Blood taken for  
    (a) Morphology  
    (b) Chemistry  
    (c) Serology.
- 11:00 A. M. Second P-S-P Collection  
Special Examinations and Consultations.
- 1:00 p. m. Patient discharged.

A light breakfast may be served after the blood specimens have been taken. By systematic arrangement several special observations and consultations, as suggested by the history and physical examination, can be performed on the morning of the test. If many observations are required, or if lengthy operations such as x-ray studies of the gastrointestinal tract or the duodenal function are required, return on a later day may be necessary. The sugar test can be carried out at home, each set of samples being sent at once to the hospital for analysis and the next dose of sugar, as indicated by the latter, sent back to the patient.

The degree of definition obtainable by the two procedures is interesting. Under present conditions, less than 3 per cent of the patients undergoing the week's study ("Long Form") are discharged as unclassified, and many of these are partly resolved. For example, five patients in this group giving data indicative of either pituitary disease or of neuro-syphilis refused the lumbar puncture, which would probably have resolved the question. Similar conditions would account for several of the remainder.

On the other hand, in a recent series of 500 patients receiving the morning study, 153 were reported at first as unclassified, and certain additional tests were requested. In 91 of these cases further study established the diagnosis. The greater part of the remaining 62 would undoubtedly have been resolved had the requested supplementary information been forthcoming.

In considering the results obtained in this series of 1,000 cases, certain facts must be borne in mind. With the large number of data involved in the evaluation of each case, a statistical

method of presentation is imperative. As, however, each diagnosis rests upon the interrelationship of the many individual facts recorded, such a general compilation in some measure defeats its own end and tends to obscure the real findings. To illustrate: A nephritis coexisting with an ovarian failure may cause a rise in blood uric acid not characteristic of the latter condition and suggesting pituitary disease, in which such an increase is really significant. In certain dysfunctional conditions the blood may be strikingly lymphoid or leucoid, depending on the type and phase of the dysfunction. In any summary these opposing conditions tend to compensate each other and mask the really significant divergences. By judicious selection, a group of extreme hypo- and hyper-functional thyroid cases could be assembled in which the algebraic sum of the basal rate deviations could be  $\pm 0$ . On the other hand, due allowance for all the factors operating entails so great a complexity in presentation as to produce an equal obscurity.

Another unavoidable and hampering condition lies in the fact that in a given group departures from the normal reflect in large degree the severity of the condition. The inclusion of a number of incipient and mild cases tends to minimize the positive definition of a trend which will be strikingly shown by the individual advanced case. In the subsequent papers in which individual glands only will be discussed, these objections are partly met by greater detail in presentation; even so, they cannot be eliminated, and in the present paper they operate in full force.

With due recognition of the unavoidable limitations of the method of presentation, the data may be discussed in detail.

As was stated earlier, the present paper aims only to present the general method with such supporting data as may be recorded in significant form. Many informative details must be reserved for the subsequent papers.

#### HISTORY

Under this caption will be considered only those points which may assume significance for the diagnosis of endocrine disease. At the risk of redundancy, the writer wishes to reiterate that there is no one of these points that may not equally be the result of some non-endocrine disease. Their incidence, however, is of

sufficient frequency to suggest possible endocrine disorder. That all episodes should be dated to establish chronological sequence, should not require comment.

(a) A family history of established endocrine disease is of interest. There seems to be what may best be described as a "constitutional tendency" for the recurrence of endocrinopathies in a given familial line. Many such are recorded in the literature, and there are several striking examples in the writer's own experience. (See Family "C," in the later Thyroid paper.) \*

(b) The patient's own past history is most significant. Many endocrine conditions seem to date from severe infections. At the present time the number of individuals who seemingly exhibit sequelae of the severe influenza of 1918 and 1919 is striking. Earlier history of jaundice may help to clarify an anomalous sugar tolerance in thyroid failure. Trauma is always suggestive if involving an area associated with an endocrine gland. Rapid changes in weight, periods of over- or undergrowth, modification in facial contour or increase in size of hands or feet, loss or overgrowth of facial and body hair, are all possibly significant. The foregoing serve merely as illustrations. Many other suggestive evidences will be found in a well compiled history, and the reader can supplement any list as his own experience warrants.

(c) Headache is a frequent finding in this group of disorders, and seemingly confined to no one of them.

(d) Progressive deafness, without demonstrable anatomical change, has been shown by Drury (8) to be associated with endocrine disease in some two-thirds of the cases studied.

(e) A fatigability wholly disproportionate to recorded mental or physical exertion seems to be a cardinal point in the endocrine picture. One hesitates to crystallize this into a formula, but in the main there is a low level of vigor on arising, an improvement to some apex as the day progresses, and then a rapid decline to a level equal to or even below that of starting. Adrenal deficiency is an exception in that rest determines the high levels and exercise their rapid subsidence.

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\* Recognition of this tendency does not imply subscription to the genial views of those writers who resolve all ethnic traits into manifestations of individual *endocrine dominance*. While such speculations are diverting, the exclusion of demonstrably powerful biologic forces, the complete absence of any objective supporting evidence, and the resolute elimination of all contradictory evidence, render them unconvincing.

(f) Gastrointestinal disturbances are frequently encountered. Ptosis, poor appetite, and constipation characterize the hypofunctional states, while the converse may obtain with hyperfunction of the pituitary, and especially the thyroid. Polydipsia and polyphagia are conventionally referred to pituitary disorders, but they may be found in both thyroid and, less frequently, ovarian cases.

(g) Unexplained pain in the lumbar region is frequently found in hypothyroid cases.

(h) The menstrual function is peculiarly susceptible to endocrine influences. Late onset of the catamenia, irregularity, scanty or profuse flow, and amenorrhoea and early menopause, are all features of endocrine disturbance. In pituitary and ovarian disease, the tendency is seemingly toward increase in the interspace with scanty flow; with the thyroid, the latter may be profuse and the rhythm increased or diminished.

(i) Sterility. For some time past the author and his associates have been carrying out elaborate studies on the numerous factors concerned in failure of reproduction. Among these, endocrine disorders take an important place, both by the determination of anatomic impedences as the result of aberrant growth, and also through functional disturbances which influence the viability of the sex cells. In this later series, the pituitary, thyroid, and gonad are apparently operative in the order named. A history of miscarriages, with chronological detail, is of primary importance.

(j) Nervous instability and irritability are again among the most common findings. Without seeking a definition which is phantastic, it may be said that the victims of ovarian failure frequently present an active, insistent egocentricity, testicular loss or failure leads to profound mental depression, and the intense nervousness of the hyperthyroid may also be found in the hypofunctional case or merge to a less aggressive selfishness that expresses itself in a sullen truculence. The pituitary patients seemingly more nearly approach the normal level of nervous balance.

(k) Speculation as to the etiology of psycho-neuroses and psychoses, in recent years, has been dominated by two schools of thought, one of which concedes only an endocrine cause, while the other with equal vigor abjures all but psychogenic back-

grounds. Both theories are probably right in some measure. Certainly the writer has studied a few cases in which a frank psychosis co-existed with an equally demonstrable endocrine malfunction; in some of these both disorders were seemingly corrected by the indicated glandular treatment. Equally, other mental cases have shown a physical normality that eliminates any endocrine disease. It is as unwarranted to express all mental disease in an endocrine formula as to deny the influence of physical conditions on the state of mind. In a subsequent paper the writer will offer one or two striking cases illustrating each contention.

Aberrations of temperature response, such as hypo- and hyperthermia, are frequently found in thyroid disease and not unknown in other endocrine states.

The above constitute some of the suggestive points which may be derived from a well-ordered history. No attempt at completeness is possible within the scope of a journal article.

#### PHYSICAL EXAMINATION

Of necessity, this section deals chiefly with trophic evidences. A principal value of the physical examination is to indicate the existence of non-endocrine disorders to which the patient's disabilities may be ascribed. Only occasionally will the findings be positively suggestive of endocrine disease.

(a) The general body habitus, and particularly the relation of individual segments to each other or to the whole, are of real significance. Draper (9) has spent years in the study of such correlations and has gathered together a massive array of data which are most suggestive. It is to be regretted that others with the same fine enthusiasm lack the temperate reserve in interpretation that marks his concluding paragraphs (l. c., p. 222). Disproportion engendered by overgrowth before epiphyseal union has taken place or, equally, by premature closure, is highly suggestive in its measureable results.

(b) The localized distribution of obesity—as the girdle type found in pituitary disease, the fat body with thin legs of the patient with ovarian failure, and the generalized distribution in the hypothyroid individuals, really constitute a part of the foregoing. True, they are seldom realized in classic type, but they do define suggestive trends. The degree of obesity may make

them all apparently merge in the thyroid type, as in a case of the writer's, a boy with pituitary failure who was less than five feet tall and weighed 400 pounds. Emaciation also may be suggestive where the loss has been selective.

(c) The amount and distribution of body hair with tendency to inversion in type of this secondary sex characteristic is significant. Each of the glands may produce one or more characteristic pictures.

(d) The spacing, development, and general appearance of the teeth should be carefully recorded. They may suggest disorders of the pituitary or thyroid or call attention to such conditions as rickets and congenital syphilis.

(e) The shape of the nose may be suggestive of an endocrinopathy. The characteristic forms in acromegaly and cretinism are illustrations.

(f) Marked asymmetry of the face and, less frequently, of other portions of the body, may suggest those growth anomalies resulting from metabolic derangement.

(g) The shape, appearance, and consistency of the finger nails undergo modification, particularly in thyroid disease.

(h) The general character of the skin and the presence of skin eruptions should always be noted. With even the meager knowledge of today, it seems possible that endocrine disease may engender certain trophic changes in the skin, possibly by indirect influence on the general metabolic level. Myxedema in thyroid failure is the prototype.

(i) A tendency toward the development of varicosities in the lower limbs has been noted in pituitary disease.

(j) Evidences of thyroid enlargement are as apt to be misleading as they are helpful. The diagnosis of thyroid disease on the unsupported evidence of a goiter has done and is doing grave mischief.

(k) Aberrations of vision can best be considered under a later caption, and this is true also of slow and rapid pulse rate, and changes of body temperature, blood pressure, and certain other physical measurements.

Again, in concluding this section, emphasis is laid on the illustrative character of the items selected, and even more strongly on the fact that they are never more than suggestive. Final diagnoses should not rest on the appearance of the eye-

brow nor on an obesity deriving from what may be designated with courtesy as a good appetite.

Turning next to the laboratory findings and with reminder of the limitations imposed by tabular summation, the relative composition of the series may be considered.

TABLE III  
DIAGNOSTIC SUMMARY

Diagnosis	Number of Cases		Per Cent	Group Per Cent
	Series B	Series S		
Not Endocrine . . .	79	211	29 0	29 0
Pituitary, hypo- (-)	28	35	6 3	
dys- (±)	113	103	21 6	28 4
hyper- (+)	5	0	0 5	
Thyroid, hypo (-).	22	50	7 2	
dys- (±).	14	21	3 5	12 4
hyper- (+)	0	17	1 7	
Gonad, hypo- (-)	55	89	14 4	14 4
Adrenal, hypo- (-)	10	3	1 3	1 3
Pluriglandular, hypo- (-)	2	2	0 4	1 8
dys- (±).	6	8	1 4	
Unclassified, endocrine doubtful	6	63	6 9	12 7
	10	48	5 8	
Totals	350	650	100 0	

Too great significance should not be given to the relative magnitude of any group. The cases were all seen in a consulting diagnostic service, and in many instances the patients did not require elaborate studies to determine the underlying etiology; thus certain classes find but scant representation in this series. This is particularly true of the hyperthyroid group in which the presenting clinical picture, with its characteristic features, together with the history, physical examination, basal metabolism, and blood morphology, usually suffice to establish the diagnosis. At the most, the abridged study (Short Form) was adequate \*

The relative infrequency of demonstrable adrenal cases is strikingly shown. These represent the residua of a much larger group submitted in which bronzed diabetes or primary anaemia was found to be the true condition.

\* In a very few subsequent cases the longer study has been carried out. In all of these, non endocrine diagnoses had been established elsewhere, and only complete investigations would permit a certain resolution of the question.

Considering the stress laid upon so-called pluriglandular syndromes, to say nothing of the widespread use of pluriglandular therapy, the figures here presented are worthy of remark. A further analysis of the eighteen cases offers yet more salient facts. These are presented in tabular form.

TABLE IV  
ANALYSIS OF PLURIGLANDULAR CASES

Gland	Surgical	Total	SUMMARY		
Involved	Cases	Cases	Etiology	No.	%
Pituitary .....	0	12	Surgical Cases.....	13	1.3
Thyroid .....	5*	11	Doubtful† .....	1	0.1
Gonads .....	10*	12	Functional or organic.	4	0.4
Unknown .....	0	1†			
			Total.....	18.	1.8

\* Two patients had both ovaries and part of the thyroid removed.

† Mongolian idiocy.

Summarized, all but five of these cases derive their plural character from the interposition of surgery, and of these one, that of a Mongolian idiot, has only a conventional claim to inclusion; a second is a patient with thyroid failure in middle age who had seemingly an overactive anterior lobe in the prepuberal years. The whole question will be discussed in detail in a subsequent paper.

A few points, only, require comment. The designation of the degrees of activity of the several glands has already been discussed.

It is significant that in a series of 1,000 cases, in the main carefully selected as presenting evidences of probable endocrine disease, nearly one-third demonstrated a definite non-endocrine condition to which the presenting symptoms could be referred.\* This fact emphasizes the unwisdom of the establishment of an endocrine diagnosis on purely clinical evidence alone, and, as a corollary, the necessity of eliminating disease condition unassociated with the ductless glands before interpreting data in terms of endocrine disease.

The incidence of pituitary cases seems to exceed either the thyroid or gonad by a ratio of 2 to 1. As has been pointed out,

\* In the next 1,000 cases the non-endocrine percentage was 39.6. This was influenced in some measure by the study of certain special disease groups to ascertain if there were an endocrine element in their etiology. Deleting these cases, the remainder constitute about one-third of the whole.



this is not strictly accurate as regards the thyroid, and the gonad figures are possibly influenced by the relative infrequency of male patients. As will be considered elsewhere (this article and a later paper on the gonads), the testicle in adult years, in contradistinction to the ovary, seemingly exercises but a meager influence on the general metabolic level. The individuals here presented were chiefly castrates, who have co-operated in the work, or were patients referred for sterility following a non-venereal disease. Within these limitations the figures as given possess a certain general significance. The predominance of the dysfunctional type of pituitary is interesting.

The larger number of unclassified cases in the "Short Form" group illustrates the value of the additional tests. Had opportunity been given for further study, many of them could have been resolved, as has been pointed out above. More extended experience also tends to make the undetermined group smaller.

The next table presents some of the purely physical measurements and illustrates the wide range of the cases studied. As these are based on absolute values, they emphasize the worst features of collective presentation. All measurements are made on the nude subject and are determined with standard anthropometric equipment. Lung volumes are measured with a calibrated water-sealed spirometer of standard type.

The numerical preponderance of the female in the endocrine group contrasts with the relatively greater equality in the non-endocrine. In the main this agrees with other records, only the pituitary proving an exception. While the tallest case is in the pituitary group, the average corresponds to that of the entire series and is less than that of the non-endocrine section. The relative average age shows that this is not referable to an undue proportion of children. The age averages are in substantial agreement with the observations of others. The slightly greater age of the pluriglandular group reflects probably the time factor in the causation of the surgical element to which they are referable. The sitting height indices show a very definite uniformity. They are influenced by the female preponderance in absolute magnitude, and striking individual departures are lost in the summary. The failure of the gonad (and the pituitary) group to show a low value is due presumably to the fact that cases presenting disease in adult years dominate the series. In the

TABLE V  
PHYSICAL MEASUREMENTS

Observation	Unit	Endocrine Group							Not End.
		Pit.	Thy.	Gon.	Adr.	Pl. Gl.	Uncl.	Total	
Sex.....	Male..... Female....	37 63	22 78	5 95	23 77	0 100	16 84	24 76	42 58
Age.....	High..... Low..... Average...	70 6 33	74 8 37	63 13 33	62 7 35	63 17 41	61 7 32	74 6 33	78 9 38
Height...	High..... Low..... Average...	195 103 164	184.5 131.5 162	174 148 162	177 115 162	188 146 166	181.5 113 160	195 103 163	193 139 165
*Sitting Height.....	High..... Low..... Average ..	100 56 87	96 75 86	94 77.5 86	96 64 85	95 80.5 88	92.5 62 85	100 56 86	99 72.5 87
Sitting Height Index.....		0.530	0.531	0.531	0.524	0.530	0.531	0.530	0.527
Chest.....	High..... Low..... Average...	150 54 81	107 62.5 80	121 60 78	107 56 73	110 63 83	111.5 50 79	150 50 80	125 59 80
Weight.....	High..... Low..... Average...	164 15.7 67.4	124.5 31.3 61.8	124.0 35.8 62.0	89.0 22.0 52.6	128.0 41.2 70.0	113.0 15.6 62.9	164.1 15.6 64.4	145.0 28.1 61.5
Area.....	Average...	1.73	1.66	1.66	1.55	1.78	1.66	1.69	1.67
†Lung Volume.....	High..... Low..... Average...	6200 600 2960	4610 820 2550	4910 930 2710	4100 1700 2460	3200 1140 2440	4520 800 2550	6200 600 2760	5500 300 3020

\*Designated as "Trunk" by Dreyer.

†Designated as "Vital Capacity" by Dreyer.

weight averages, the pituitary and pluriglandular groups (in the latter a pituitary influence is dominant) are well above the mean, while the emaciation of the adrenal cases is equally clearly defined. All of the endocrine cases save the pituitary, show values for the lung volume significantly below the non-endocrine group. Absolute values here are influenced by several extraneous factors which do not appear. The seeming diminution is in part apparent rather than real (see adrenal cases in next table), and in the main is probably due to the asthenia which is a character-

TABLE VI  
"VITAL CAPACITY" COMPARISONS

Observation	Endocrine							Not End.
	Pit.	Thy.	Gon.	Adr.	Pl. Gl.	Uncl.	Total	
Weight—								
High.....	+217%	+82%	+107%	+19%	+78%	+67%	+247%	+75%
Low.....	-42%	-29%	-37%	-36%	-14%	-36%	-42%	-35%
% above normal..	62	57	55	25	65	55	58	48
Average.....	+29%	+23%	+24%	+16%	+21%	+26%	+26%	+17%
% below normal..	38	43	45	75	35	45	42	52
Average.....	-12%	-15%	-11%	-19%	-9%	-13%	-13%	-12%
Total average*..	+13%	+8%	+9%	-10%	+12%	+9%	+10%	+2%
Chest—								
High.....	+96%	+36%	+66%	+15%	+43%	+47%	+96%	+36%
Low.....	-24%	-23%	-17%	-17%	-18%	-13%	-24%	-23%
% above normal..	64	53	47	25	75	60	57	58
Average.....	+12%	+12%	+13%	+12%	+16%	+14%	+13%	+9%
% below normal...	36	47	53	75	25	40	43	42
Average.....	-7%	-7%	-7%	-10%	-10%	-7%	-7%	-7%
Total average*..	+5%	+3%	+2%	-5%	+10%	+5%	+4%	+2%
Lung Volume—								
High.....	+18%	+12%	+23%	± 0%	-11%	+17%	+23%	+17%
Low.....	-62%	-75%	-67%	-29%	-60%	-58%	-75%	-89%
% above normal..	11	9	10	8	0	6	10	17
Average.....	+6%	+7%	+7%	± 0%	-0%	+12%	+7%	+5%
% below normal...	89	91	90	92	100	94	90	83
Average.....	-22%	-28%	-22%	-19%	-27%	-24%	-23%	-26%
Total average*..	-19%	-25%	-20%	-17%	-27%	-22%	-21%	-21%

\*Weighted for number of cases.

istic of endocrine disease in general. As was stated above, in many cases absolute average values are not greatly informing; relative quantities tend to place greater emphasis on significant differences. In the next table are collated values derived from the Dreyer (10) and West (11) comparisons. With the former, only those correlations based upon sitting height ("trunk") are considered, as the author's formulation presupposes a relatively normal configuration, and in cases of obesity leads to impossible extrapolations. Further, but one occupational standard instead of Dreyer's three has been used, as by so doing disturbing com-

plications are avoided. The whole matter has been discussed by the writer (12) in another place. Experience in this country shows that the "A" male and "B" female standards most nearly conform to average experience. In the West comparisons, for like reasons, only the male and female standards are used. In both series, children (boys and girls) are referred to the female standards, as experience has shown this to be most representative. The values presented in the table for Lung Volume ("vital capacity") are the averages of the Dreyer and West comparisons.

In the table above, "High" and "Low" represent the deviation from prediction in the two extreme cases in the group. The relative number of the group above and below prediction are indicated by percentages and the average deviation of each group is appropriately placed. The total average is the algebraic summation of the two groups suitably weighted for numbers. To illustrate, the heaviest pituitary case was 247 per cent above prediction (+), and the lightest 42 per cent below (—). Sixty-two per cent of the group were overweight, the average being 29 per cent above prediction (+), while the remaining 38 per cent were underweight, their average being 12 per cent below prediction (—). The whole pituitary group showed an average of 13 per cent above (+) prediction.

With the weight comparisons, the dominance of the pituitary and pluriglandular groups in part disappears, but the emaciation of the adrenal cases gains in emphasis. The chest values are indeterminate. The lung volumes in the total endocrine group exactly equal those in the non-endocrine. Of the individual components of the endocrine group, the thyroid and pluriglandular groups are most affected, the pituitary and, surprisingly, the adrenal\* the least. The lowered lung capacity in the thyroid cases has already been commented on, and a number of years ago Bryson (13) called attention to the lessened chest expansion in thyroid disease. With the pluriglandular group it is possible that the low values reflect the influence of the twofold endocrine disorder which they present. Too great weight should not be placed upon lung capacity measurements, however, since the degree of co-operation of the subject influences the magnitude unduly. It is safe to say, nevertheless, that thyroid disease

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\* The small number of cases composing this group makes this observation less significant than in the case of values for the other series.

causes a diminution in this quantity that is of potential diagnostic significance.

The general examination of the urine offers numerous points of interest. Many of them cannot be reduced to presentation in tabular form, but certain significant measurements are grouped in the next table. Of the methods selected, that of Ehrlich (14) for the so-called "urobilinogen," the amylase method (15) \* and the standard method for salol may be mentioned. The values for the "phthalein" test were obtained by comparisons with graded standards in a du Boseq colorimeter. The urea curve was determined by four two-hour collections following a test meal of 15 grams of pure urea taken in a fasting state and following a two-hour control collection. Folin's (16) method was used for the analyses.

TABLE VII.

URINE DATA

	Endocrine						Not
Observation	Pit.	Thy.	Gon.	Adr.	Pl. Gl.	Uncl.	End.
Volume ..... Av.	1230	1110	1130	1140	1440	1220	1260
Specific Gravity. Av.	1.019	1.019	1.019	1.016	1.016	1.019	1.018
Albumin, % positive	22	20	19	69	28	9	17
Casts, % positive	16	16	17	23	11	13	15
Sugar, % positive	24	12	27	23	33	16	10
"Urobilinogen"							
% positive	36	3	0	0	22	16	2
Amylase Index. Av.	18	16	16	13	18	11	14
Salol (minutes) . Av.	74	91	88	96	90	61	79
Urea Curve, Normal	71%	80%	86%	28%	83%	..	80%
Low	29%	20%	14%	72%	17%	..	20%
P-S-P,** 2-hour							
Total Av.....	50%	55%	54%	50%	53%	53%	53%

Considering first the urine volumes, it is evident that the pituitary does not exhibit any striking augmenting influence. Naturally, in the series a number of patients exhibited polyuria, but a compensating oliguria was shown by others. As the work of Camus and Roussy (17), Houssaye (18) and, most recently, Bourquin (19) has thrown some doubt on the unique influence of the pituitary as the direct causative agent in diabetes insipidus, this is rather to be expected. The lowering influence of

\* Later discontinued, as other methods of evaluating kidney function were found to be far more significant.

\*\* Phenolsulphonephthalein.

thyroid and adrenal failure is here shown as a tendency. The low gonad value is in part ascribable to the overwhelming predominance of females coupled undoubtedly with a tendency to lessened elimination. Only the adrenal group shows a marked decrease of dissolved matter ("total solids"), though many individual cases of thyroid failure exhibit the same tendency. The healthy appetite of many of the thyroid subjects tends to mask the lowered metabolic level which undoubtedly exists in failure of this gland. It will be remembered that the hyperthyroid group in this study is too small to influence the summated results. While albuminuria is a frequent observation in the entire series, its dominance—and in less degree the incidence of casts—in the adrenal cases is a marked evidence of the nephritis, which is a usual feature of this condition. In general, however, in the endocrine cases, albumin and casts may be regarded rather as evidences of disturbed kidney metabolism than as indicating the existence of true nephritic states.\* A striking observation is the relative frequency of glycosuria in the endocrine group. Overactivity of the posterior lobe of the pituitary (but not underactivity as recorded by several writers), hyper- and dys-functional states of the thyroid, and ovarian failure have frequently been recorded as causal conditions. The lower percentage in the thyroid group rests on the relatively lesser influence of this gland on carbohydrate metabolism. This will be considered later under "Sugar Tolerance." The writer's findings with adrenal failures are not in accord with the frequently expressed opinion that this condition raises sugar tolerance. Reference will be made to this point later, both in this and in a subsequent paper. Another interesting feature is the not infrequent appearance of glycosuria in the non-endocrine group. It is to be remembered that pancreatic cases were excluded from this compilation. The easy assumption, so frequently recorded, that glycosuria indicates an incipient diabetes (that of pregnancy, for example) is but a persistence of the erroneous concept of unitary control of body functions. Lesions of the central nervous system (without other evidence of indirect pituitary involvement), syphilis, liver disease, primary anaemia, leukaemia, and cancer, are all represented in the group

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\* In the subsequent paper on the thyroid, emphasis will be laid on the "pseudo-nephritis," which we have already recorded in this condition.

here recorded. This question, too, will be discussed in detail in a later paper.

A positive "urobilinogen" test stands out definitely in the pituitary group or in those series such as the pluriglandular and "unclassified" in which this gland is or could be a factor. In the positive thyroid cases there was a concomitant liver dysfunction, while this latter condition and primary anaemia were responsible for its appearance in the few non-endocrine cases. When they can be excluded, the test offers one fact toward a pituitary diagnosis. The non-specificity of the test as an evidence of the presence of urobilinogen has already been touched upon.

The amylase test falls short of any real significance and in the later studies has been discontinued. Salol is a rough measure of gastric motility, if kidney function be demonstrated to be normal. It is included for its possible information in the sugar tolerance test. The lowered kidney permeability of the adrenal cases is also revealed in the urea curve. The observations of this laboratory would indicate that an inadequate level of protein metabolism may be a source of error in the results of this test. Whether through tissue absorption of urea or through some other agency, the fact remains that many patients with a partial protein inanition and demonstrably sound kidney function show a low curve of urea elimination under the stimulus of a provocative urea test meal. Blood urea measurements recorded elsewhere (20) indicate that this is not due to failure or delay of absorption. The observed fact is suggestive. The phenolsulphonephthalein values seem only to illustrate the relatively inconclusive character of this test in all but terminal phases of kidney involvement.

Another observation based upon the determination of urine constituents is found in the so-called "nitrogen partition." While under ordinary conditions urea constitutes the major portion of the protein waste, uric acid, creatinin, and ammonia are constantly present\* in appreciable amounts, representing end phases of specialized metabolic processes. In addition, there is the undetermined fraction made up of a large number of both known and unknown nitrogen-containing compounds usually

\* Exception is noted of the disappearance of the last named when the combining power of the plasma exceeds 80 volumes per cent. (See Fitz and Van Slyke.) (21).

present in small amounts. It should be repeated that this test as performed in this study does not constitute a part of an elaborate nitrogen balance measurement. The first urine examined gives information both as to the daily dietary of the patient and the relative composition of the protein waste. When a second urine is tested—as in the routine of the Long Form—it gives the added information of the influence of the hospital standard dietary on the quantitative performance of the patient, and serves as a check on the first. In the first instance, the total gives valuable evidence on the accuracy of the patient's statement of dietary habit,\* and in the second, as will be shown, the items of the partition may assume a diagnostic significance. Total nitrogen is determined by the standard modified macro-Kjehldahl method (using both copper and potassium sulphates), urea, uric acid, creatinin, and ammonia by the several procedures devised by Folin (22). The data are collected in the next table.

TABLE VIII  
NITROGEN PARTITION

Observation	Endocrine							Not
Tot. Nitrogen. (gms.)	Pit.	Thy.	Gon.	Adr.	Pl.Gl.	Uncl.	Tot.	End.
Urea “ (%)	80.6	79.0	80.9	79.8	80.0	80.7	80.3	81.1
Uric Acid “ (%)	2.0	2.2	2.0	2.2	2.1	2.0	2.1	2.3
Ammonia “ (%)	3.9	4.2	3.9	4.7	4.9	3.6	4.0	3.8
Creatinin “ (%)	4.4	4.2	4.5	4.0	4.8	4.2	4.3	4.5
Residual “ (%)	9.1	10.4	8.7	9.3	8.2	9.5	9.3	8.3
Residual, total % of cases equal or over 9%	45	56	45	54	44	61	49	38

In the table given above, the first line records the average nitrogen elimination of the individuals composing each group, while the next five indicate the percentage distribution among the five components. The last line records that part of the group exhibiting a “residual” or “undetermined” fraction in excess of the conventional normal of 9 per cent. For example, 56 per cent of the thyroid cases showed residual fractions above the normal.

All of the total nitrogen values here presented are above

\* This ranges in experience from the obese lady who confesses to one egg and a biscuit or two a day, with 20 grams of nitrogen in the urine, to the equally subjective individual who claims a liberal dietary habit—and shows 3 grams. Body weight is not a safe criterion for estimating protein levels, and a partial inanition of this essential constituent influences significantly the basal rate, the blood chemistry, and other important magnitudes.



the maintenance level and all of them are likewise below that which would correspond to the hospital allowance of protein. (Based on the protein allowance in terms of body weight, this would range approximately from 11 grams in the adrenal cases to 15 grams in the pluriglandular). The discrepancy becomes less when it is remembered that two-thirds of the patients collected their urines at home and that the first urine of the remainder was collected in such manner as to show the home nutritional level. A lowered level of protein metabolism in thyroid and pituitary failure has often been recorded, while the increase in hyperthyroidism is regarded as pathognomonic. The thyroid hypofunction effect is shown here, but an adrenal influence appears even more strikingly. Lowered kidney permeability and the several influences due to asthenia undoubtedly operate here. The pituitary shows the highest level of the several groups, bulimia being one probable factor, but the existence of a generally normal level of many functions in this particular condition being certainly another. In passing, it may be said that while the several types of pituitary disease cause certain strikingly significant departures from the normal, in a number of respects they conform straitly to conventional standards. The differential significance of this will be stressed later.

Turning to the several partition formulas, the only striking irregularity is found in the residual or undetermined moiety. Passing comment may be made on the constancy of the uric acid fraction, a constituent which Falta (23) found to be increased in the pituitary cases, but which is not demonstrably influenced in this series.

The average value for the residual fraction in normal adults drawn from nearly 400 cases [Folin (24), Mathews (25), Long and Gephart (26), Rowe and Proctor (27)] is just under 6 per cent, with 10.9 grams as the average for the total nitrogen. Folin's original study demonstrated an increase in the relative amount of the residual nitrogen with lowered nitrogen elimination, but the percentage remains less than eight when the nitrogen elimination exceeds five grams. It is true that the residual fraction is determined by difference and so absorbs all of the errors incident to the other measurements, but these would operate equally in all groups large enough to nullify individual differences. Hence such variations as are actually observed must

be significant even though the absolute magnitude may not be rigorously accurate. Further, the use of the best available methods by a group of technically skillful workers offers additional safeguard against gross error. The experience of the writer with several thousand such analyses has led to the adoption of the conventional value of 9 per cent as the upper normal level. Conceivably, this is slightly high, but the adoption of a somewhat lower criterion would serve only to emphasize the endocrine influence. As it is, the endocrine series shows an upward tendency most marked in the thyroid group, which also exhibits the largest percentage of individual cases exceeding the conventional normal limit.\* The adrenal comes next and only the pluriglandular group shows an average less than the non-endocrine. Even here the percentage of individual cases showing high values is greater in the endocrine group. Further, the endocrine average is above, that of the non-endocrine group below, the conventional boundary. As the percentage of non-endocrine cases showing high residuals is not strikingly inferior to that of the endocrine group, however, a further analysis of the former is interesting.

Cases of leukaemia, malignant neoplasm, tuberculosis, and epilepsy show very high incidence and very high absolute values. Lower, but still significant, are primary focal infections, such as those of teeth and of tonsils, various lesions of the central nervous system, and primary anaemias.

The underlying mechanisms of this increase are still obscure. A study already reported in brief [Rowe and Proctor (27)], and shortly to appear in detail, demonstrates that while the amino-acid, hippuric acid and creatin fractions all show increase—the first, only, in significant absolute amount—there still remains an undetermined quantity which in the control (normal) group is 3 per cent, in the non-endocrine group about 5 per cent, and in the endocrine group exceeds 7 per cent of the total nitrogen elimination. Further, a determination of the neutral sulphur fraction (as possibly associated with nitrogen-containing molecules) shows no change of significant proportions. In other words, while known constituents of the urine, usually present in small amount, are found to be definitely increased, there remains

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\* The unclassified cases are, for obvious reasons, omitted from this discussion.

a fraction of unknown composition still to be accounted for. This problem is now under investigation.

As the urine constituents are derived from those of the blood stream, the chemical composition of the latter may next be considered. The routine examination calls for the determination of four nitrogenous constituents and of sugar. Individual cases call for additional observations, but in no series has any other single constituent been measured with sufficient frequency to warrant inclusion.

In the main, the methods outlined in the well-known Folin-Wu (28) procedure have been followed. Urea has been aerated rather than distilled, though both methods are used to control each other. The uric acid method has been varied in accordance with the suggestions later reported (29).

Neither the uric acid nor creatinin procedures are specific for the substances named, and this criticism is equally applicable to the sugar determinations. They all, however, give dependable and reproducible results, seemingly are not grossly in error, and the relative values thus obtained are to be regarded as significant. The collected data are given in Table IX.

TABLE IX

BLOOD CHEMISTRY (and Serology)

Observation	Endocrine						Not
	Pit.	Thy.	Gon.	Adr.	P. G.	Uncl.	End.
Non-Protein Nitrogen..mgm.	33	32	31	38	31	32	34
% over 35 mgm.....	29	26	20	58	25	24	26
Urea Nitrogen.....mgm.	16	15	14	14	16	14	16
% over 17 mgm.....	17	20	19	18	19	10	24
Uric Acid.....mgm.	3.8	3.5	3.3	3.8	3.6	3.4	3.5
% = or over 4.0 mgm. (net) *	34	18	12	22	20	25	11
Creatinin .....mgm.	1.5	1.5	1.5	1.5	1.5	1.6	1.5
Residual Nitrogen....mgm.	15.1	15.2	15.3	22.1	13.2	16.2	16.2
Sugar .....mgm.	94	98	97	84	96	95	97
% over 120 mgm.....	1	4	4	0	6	2	2
% under 80 mgm.....	5	5	8	50	12	8	5
+ Wassermann .....(cases)	0	1	0	0	1	0	10
+ Schwartz-McNeil .(cases)	1	0	0	0	0	0	0
+ Spinal Fluid.....(cases)	1	0	0	0	0	0	2

\*All demonstrated cases of nephritis deducted.

In largest measure the blood picture confirms the observations already made on the urine. Significant variation is shown by the high uric acid in pituitary disease. This is duplicated only in the adrenal group, and here are found other evidences

of kidney disease which are lacking in the pituitary picture. The high residual fraction in the adrenal group is a striking observation possibly connected with the urine findings in these cases. No explanation for the low value in the pluriglandular group is at present known. The relatively greater frequency of high blood uric acid without demonstrable kidney disease lends to the datum a certain diagnostic significance. Hammett and his co-workers (30) observed this phenomenon in a small group of experiments with pituitary feeding. Whether it is due to an increase in uric acid or of some other substance giving the same reaction, remains to be ascertained.\*

The hypoglycaemia of adrenal failure, frequently reported, is definitely confirmed in this series. That blood sugars are relatively normal in all of the other endocrine conditions renders this a point of significance for differential diagnosis.

The results of the serological examinations, included in this table for convenience, show nothing striking. The inclusion of the three positive cases in the endocrine group is reasonable, as the pituitary case with positive spinal fluid gave only a doubtful test, while the positive Wassermanns in the single thyroid and pluriglandular cases showed a possible lues superimposed upon unmistakable endocrine disease.

Relatively few reports of blood chemistry in endocrine disease are found in the literature, but the older art and science of blood counting has developed certain conventional formulas for the blood morphology. The lymphocytosis in thyroid, pituitary, and adrenal malfunctions, the eosinophile increase in the two latter, and the increase in large mononuclear cells in thyroid disease have been frequently recorded. Less certainly established are lowered haemoglobin in thyroid and pituitary failure, lowered red count in these and adrenal failure, and leucopenia in the first two. A prevailing high red count has been remarked in acromegaly. The results in this study are grouped in Table X.

No striking deviation in the haemoglobin content is exhibited by any of the groups. The primary anaemia cases were too few to influence the average in the non-endocrine group. The red count shows a surprising uniformity. Naturally, individual cases with well-marked secondary anaemia are absorbed in the

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\* In a few observations by the modified Folin method (31), the uric acid amounts continued relatively high.

TABLE X  
BLOOD MORPHOLOGY

Observation	Endocrine						Not
	Pit.	Thy.	Gon.	Adr.	Pl.Gl.	Uncl.	End.
Haemoglobin, %.....	89	87	90	87	91	90	88
Erythrocytes (1,000,000)...	5.11	4.92	4.98	4.79	5.09	4.95	4.93
Leucocytes (1,000).....	7.7	7.7	7.7	7.0	7.7	7.2	8.0

DIFFERENTIAL COUNT

Polymorph. Neutrophiles, %	57	56	57	51	59	57	62
% = or over 75 %.....	5	3	6	8	6	3	7
Lymphocytes .....	35	37	35	40	35	35	30
% = or over 33 %.....	58	61	54	62	65	59	38
Eosinophiles .....	3	2	2	2	1	2	2
% = or over 3% (net)*.	30	25	21	39	6	17	14
Endothelial Leucocytes....	5	5	6	7	5	5	6
Abnormal Erythrocytes...	0.5%	2%	0	0	0	0	2%

average, but with so large a number the tendency toward relative normality would seem to be established. The leucocyte counts are a low normal, in every case somewhat below the non-endocrine group, and reaching possibly significant proportions only in the adrenal cases. The cases of leukaemia were omitted from consideration in deriving the leucocyte formula. An upward trend of the lymphocytes is unmistakable throughout the entire endocrine group, and is most marked in the pluriglandular fraction. Slightly over one-third of the non-endocrine cases show a lymphocytosis as against about 60% for the endocrine group. Pituitary disease seemingly tends to produce a mild eosinophilia, while two-fifths of the adrenal cases exhibit it. A like influence is somewhat less strongly shown in the thyroid section. Broadly speaking, the chief departures from the normal are a general trend toward lymphoid bloods and a slight eosinophilia more marked in pituitary and adrenal cases. As a matter of fact, the eosinophilia in pituitary disease is in our experience somewhat more striking than the tabulation would indicate. It suggests a tendency, however, rather than an established condition. The increase in lymphocytes in the non-endocrine cases shows certain well-marked etiological relations. Malignant neoplasms, tuberculosis, focal infections, syphilis, and the blood diseases, exhibit the condition in a significant percentage of the cases observed. As will be remembered, these are substantially the same condi-

\* All cases showing acute inflammatory process, skin eruptions, protein sensitivity, and intestinal parasites, were omitted.

tions in which the interesting but non-specific high residual nitrogen fraction was manifested. In the endocrine group over 50 percent of the cases exhibit one or both of these anomalies, while nearly 40 percent of the non-endocrine fraction show the same deviation. The correlation of the incidence of these two abnormalities is interesting.

TABLE XI  
CORRELATION OF HIGH RESIDUAL NITROGEN AND  
LYMPHOCYTES

DIAGNOSTIC GROUP	Residual Nitrogen Lymphocytes	Above Normal Normal	Normal Above Normal	Above Normal Above Normal
Endocrine				
Pituitary .....	(%)	17	30	28
Thyroid .....	(%)	21	26	36
Gonads .....	(%)	20	27	26
Adrenals .....	(%)	23	31	31
Pluriglandular .....	(%)	12	35	29
Total Endocrine* .....	(%)	19	30	30
Not Endocrine .....	(%)	25	25	13

Inspection of the table shows that in the endocrine group there is a relatively low incidence of high residual nitrogen alone. Patients showing lymphocytosis, and those in whom both appear are practically 50 percent more frequent in occurrence. The non-endocrine group exhibits an opposite relation as the coincidence of the two abnormal findings is but half of the incidence of each alone. We make no attempt at this time to explain the significance of this observation. The facts are reported as they occur. It may be permitted to comment, however, that on the basis of probability, cases showing both are about 2.5 times as likely to demonstrate an endocrine etiology."

During recent years the respiratory metabolism has played a most important part in the evaluation of endocrine conditions. The establishment of normal levels begun by Atwater and Benedict (32) and continued by the latter and his later associates, in a long series of fundamental contributions, has made possible the determination of the significant variations produced by disease. Studies of the influence of disease on oxygen consumption,

\* Unweighted averages. Weighting gives the practically identical values of 19-28-30.

\*\* The unclassified cases, the great majority of which were probably endocrine, show the values 18-21-34. The endocrine element is here manifested as a tendency.

practically initiated by Magnus Levy (33), but developed principally by Du Bois and his associates (34), have shown that deviations of the so-called basal metabolism may assume a most important diagnostic significance. The profound influence exercised by the various types of thyroid disease has somewhat overshadowed, in the minds of many, the definite influence exercised by other members of the endocrine group as well as by a variety of disease states unassociated with the ductless glands.

Two clinical methods are available for this measurement, both depending on the measurement of the gas exchange. In the open circuit procedure the expired gases are analyzed both for carbon dioxide and for oxygen and the energy exchange calculated from the oxygen consumption, with due allowance for the ratio of the two. In the closed circuit method, oxygen is re-breathed after removal of the expired carbon dioxide and the energy exchange calculated from the oxygen as measured, with the assumption of a constant (0.82) respiratory quotient.\* Both methods number staunch supporters among the productive workers of this country and much polemical literature exists in which the relative merits of each are vigorously discussed. A review of this controversy can find no place in such a presentation as the present. We use the closed circuit method in our laboratories as the result of selection after long study of the problem. As in method, so in normal standards, two schools of practice exist.\*\* Both take due cognizance of the variables of age and sex, but the Harris-Benedict formula (36) correlates with standing height and body weight, while the Aub-Du Bois equation (37) determines body area (calculated from the foregoing) as the third element of mutation. Again, the merits of each have been widely discussed. The practice of this laboratory is to compare the observed value with those predicted by each formula and report the mean as the probable deviation.

Before turning to the numerical data two points should be emphasized. First, all measurements are supposedly made on individuals in a basal state, i e., post-absorptive and both physically and mentally relaxed. Both methods are influenced equally by

\* The methods basing the calculation of the metabolic rate on the carbon dioxide output alone are so susceptible of error as to find no place in this discussion.

\*\* Dreyer's (35) original suggestion of the use of body weight alone, offers no advantage, and the later generalization, based on calculated weight, is inapplicable to the clinical problem through the frequent departure of the patient from the arbitrary standards implicit therein [see (12)].

failure to observe these provisions and may easily present values which are definitely misleading. As all such errors tend to raise the observed basal rate, all measurements should be regarded as maxima with the true energy requirement of the patient equal to or less than that recorded, the degree of deviation depending upon the attendant circumstances. Second, the test should be applied under standard controlled conditions and a series of supplementary physical measurements such as pulse rate, temperature, and blood pressure, should always form a part of the laboratory record. The correlation of these data with the observed rate will frequently furnish evidence of the presence of vitiating conditions which might otherwise pass unnoticed. The conventional practice to allow for individual variation is to define the normal limits as  $\pm 10$  percent from prediction. In view of the uniform tendency of error to augment the observed values we feel that  $-10$  percent defines a definite hypofunctional trend, while equally we incline toward  $+15$  percent as the preferable superior limit. In every case such conventional boundaries must never be regarded as sharply defined. In the interpretation of borderline basal rates, many concomitant observations must be taken into consideration; no single test in itself, except under most unusual conditions, is competent to establish a positive diagnosis. Its interpretation in the light of numerous other and independent records of fact lends a necessary authority not intrinsic in its own absolute magnitude. Finally, while the operation includes mechanical features, a machine-like freedom from error is far from implicit in the procedure. The sources of error are numerous and they can be held within reasonable limits only by intelligent and scrupulous care. The data for this series are given in Table XII.

With the basal metabolism data the same conventions are observed as in the presentation of the data of Table VI ("Vital Capacity"). The last three horizontal columns give the percentage distribution of the group into those above, below, and within the conventional normal limits. The presentation of the data of the other measurements does not require explanation.

Beginning with the hypofunctional group, only the gonad and adrenal cases show values above predicted levels, and in no case does the upper deviation exceed normal limits. In the case of the gonad failures, as noted earlier in the text, marked



TABLE XII  
RESPIRATORY METABOLISM DATA

Observation	Endocrine														Not End.
	In Glandular Depression						In Glandular Dysfunction				In Glandular Hyperactivity				
	Pit.	Thy.	Gon.	Adr.	Pl. Gl.	Sum.†	Pit.	Thy.	Pl. Gl.	Uncl.	Sum.†	Pit.	Thy.	Sum.†	
Basal Metabolism—															
High.....	-4	-10	+0	+4	-29	+9	+33	+18	+7	+18	+33	+23	+87	+87	+27*
Low.....	-24	-50	-25	-30	-30	-50	-28	-25	-34	-24	-34	+15	+19	+15	-22
% above prediction...	0	0	8	15	0	5	11	24	21	15	18	100	100	100	48
Average.....	—	—	+5	+4	—	—	+8	+10	+6	+9	+8	+19	+45	+32	+7
% below prediction...	100	100	92	85	100	95	89	76	70	85	82	0	0	0	52
Average.....	-15	-23	-13	-14	-30	-19	-12	-14	-12	-12	-13	0	0	0	-6
% above +10%.....	0	0	0	0	0	0	2	7	0	5	4	100	100	100	-7
% between +10% and -10%.....	23	0	35	62	0	24	42	45	57	37	45	0	0	0	81
% = or below -10%.....	77	100	65	38	100	76	56	48	43	58	51	0	0	0	12
Temperature—Average.....	98.0	97.9	98.1	98.1	97.0	97.8	98.0	98.1	98.2	97.9	98.1	98.2	98.2	98.2	98.1
Blood Pressure, Systolic—															
Average mm.....	118	112	112	95	111	112	111	122	133	115	120	161	138	150	125
% = or over 150 mm....	0	1	3	0	0	1	4	6	36	3	3	60	31	46	12
% = or under 110 mm....	21	53	60	100	75	62	39	23	21	54	34	0	13	7	10
Diastolic—Average mm.....	73	72	69	53	68	67	73	74	81	69	74	92	73	83	75
% = or over 100 mm....	2	1	1	0	0	1	3	6	21	0	8	40	13	27	7
% = or under 65 mm....	23	28	36	100	25	42	20	20	21	35	24	20	44	32	22
Pulse—															
Average.....	71	69	74	75	69	72	72	77	76	74	75	81	101	91	76
% = or over 80.....	23	13	34	46	33	30	21	40	43	26	33	60	76	68	36
% = or under 70.....	60	58	37	38	67	52	41	23	43	43	38	20	0	10	34
Respiration—															
Average.....	14	15	16	15	18	16	15	16	16	16	16	13	18	16	15
% = or over 20.....	3	7	10	8	67	19	14	14	29	20	19	0	41	21	16
% = or under 10.....	10	4	8	8	0	6	8	0	14	7	5	0	12	6	12
Alveolar CO—															
Average mm.....	39	37	34	36	32	36	38	36	36	34	36	38	36	37	37
% over 35 mm....	46	62	54	42	33	47	55	49	36	38	45	75	67	71	48
% = or under 30 mm....	7	9	35	8	33	18	4	12	29	28	18	0	20	10	13

\*Lymphatic Leukæmia. (Summaries are not weighted for number of cases composing each group.)

nervous instability is a common feature. As we frequently have had occasion to observe, emotion, even when controlled, may cause an increase in the observed oxygen consumption which can readily assume vitiating proportions.

In the adrenal cases there is a response to fatigue which operates in the same way. As pointed out above, basal rates as observed are maxima with the true value in certain cases lying well below that recorded. Another possible explanation for the exceptions in both series may lie in our inability to define a dysfunctional state. With due cognizance of the downward trend of the energy exchange, the relative magnitudes become suggestive. Recognizing the reenforcing influence that malnutrition may exert in this group (the adrenal cases particularly), it is still apparent that the thyroid exercises the dominant influence, the pituitary and gonad the least, while the adrenal occupies a position between these extremes. The further analysis shows the adrenal to be the only member of the group in which a majority of the cases fall within the conventional limits of normality. Each of these glands will be discussed independently in later papers.

Continuing with the basal rate observations, the dysfunctional group next claims attention. Only the pituitary and thyroid of the single entities are here represented and, as could be predicted, values are found both above and below the calculated norms. The thyroid shows a series of levels produced by the intermediate transitional phases. The pituitary group includes not only such conditions but also those in which the dysfunction is caused by a difference in functional level in the two lobes. This possibility (i. e., of severe malfunction of one lobe) determines the somewhat greater scatter of the pituitary data than those of the thyroid. In the pluriglandular group one composing element is definitely hypo- (ablation) and the other dysfunctional, the summation giving predominance to the downward trend. As has already been noted, in many endocrine conditions there is a distinct tendency for an initial over-active state to undergo a functional involution toward a final condition of hypo-activity. This is shown in the separation of the data given above into the three zones of over-, normal, and under-activity.

The hyperfunctional group contains but pituitary and thyroid cases. The results are clear-cut and require but little dis-

cussion. The greater influence of thyroid disease on the energy requirement is unmistakably evident. The extremes in the non-endocrine group compare favorably with the values of the dysfunctional moiety. The highest levels are recorded in cases of lymphatic leukaemia, the lowest in malnutrition. Sharp differentiation from the endocrine group comes in the zonal distribution, with 81 per cent falling inside the limits of normality. The relative rarity in this series of those non-endocrine conditions (malnutrition, nephritis with severe edema, febrile states, and leukaemias), which significantly influence the respiratory exchange determines this division.

The temperature values in the several divisions are peculiarly influenced by the undesirable feature of this method of presentation. Slight differences, therefore, are significant. In the hypo-function group, the gonad and adrenal agree with the non-endocrine average, while a downward tendency is shown by the thyroid, which is less marked in the pituitary. The pluriglandular group exhibits the addition effect of the two endocrine agencies involved. In the dysfunctional group the thyroid and pluriglandular units show an upward tendency which, in the case of the thyroid, is emphasized by the state of hyperfunction.

As to blood pressure changes, hypofunction of the pituitary causes mild, of the adrenal severe, hypotension, the thyroid and gonad groups occupy an intermediate position. It is interesting that the late cases of hypothyroidism with arteriosclerosis fail to influence significantly the general average. The dysfunctional group shows upward tendencies, with the exception of the pituitary. The dual character of the gland, with its dysfunction including possibly severe aberration in but one lobe, probably explains the seeming contradiction. The wider limits of variation shown by the basal rate support this view. In the hyperfunctional group the upward progress of the thyroid continues moderately, while the few pituitary cases assume a real hypertensive level. It is doubtful if a larger series would exhibit so marked a degree of increased blood pressure. In the present instance, one severe case could influence the average perceptibly. Actually, three of the five cases presented *hyper-* and the other two *hypo-*tension.

The pulse rates repeat the temperature relationships, with the thyroid showing the major degrees of variation. The respiration rates show a very general uniformity, only the thyroid manifesting any real increase with increasing functional activity.

Throughout the discussion on respiratory metabolism no attention has been paid to the non-endocrine group. A general normal tendency exists and the magnitudes observed are not remarkable.

Alveolar carbon dioxide is regarded primarily as an index of the combining power of the plasma. Two methods for its determination are in general clinical use, *i. e.*, that of Marriott (38), which approximates venous, and that of Fredericia (39), which more nearly expresses arterial tensions. For reasons given elsewhere (40), we prefer the latter method, and the values here recorded are all derived by it. Venous tensions would show values a few millimeters higher. The test is at best a rough one and is peculiarly susceptible to error through incooperation. Failure to expel a representative sample will inevitably lead to low values because of dilution of the alveolar air with dead or even tidal air. While all of the averages are low, only the gonad failures and the pluriglandular group in which castrates predominate show really depressed levels. The same condition obtains in pregnancy, as has been shown by the writer (40) and others, and is of potential diagnostic significance in a study like the present. Low values arising in the presence of ketosis are shown by urine examination, and a retention acidosis caused by severe nephritis is implied where the major condition has been shown to exist.

The sole remaining test of this initial group which remains to be considered is that of the sugar tolerance. For reasons discussed in detail elsewhere (41) we have selected galactose as the material for the test meal. The technique of the test has already been described. Briefly, graded doses of the sugar are administered under standard conditions, and the assimilation limit defined by the quantity necessary to produce a transitory melituria. This is, in essence, the original Hofmeister (42) technique. Blood sugar curves have been discarded (20) as relatively meaningless and lacking the essential quantitative character. The preliminary studies (43) defined 30 grams as

the tolerance dose for the normal male under all conditions, while the normal female assimilation limit varies from 20 to 40 grams, depending upon her state of sexual maturity. The reasons for this intrinsic sex difference need not be discussed here; the fact is of very marked differential diagnostic value. Briefly outlined, in prepubertal years the female gives slight melituria with 20 grams; with the onset of menstruation the assimilation limit increases and usually in the course of a year reaches 40, the normal adult tolerance. This continues to the menopause, when there seems to be a tendency to regress to an intermediate level of 30 grams.\*

During adult years pregnancy will cause a fall in the tolerance, first to 30 and later to 20 grams. A further fall, post-partum, is transitory, and ultimately the normal level is resumed. Menstruation itself shows a tendency to lower the tolerance slightly during the period. Removal of the ovaries restores the prepubertal level of 20 grams.

Since the normal standard for the female is variable and dependent upon the level of ovarian activity, the collective presentation of results from patients representing all of the several developmental stadia must be in relative and not absolute terms. For example, a 40-gram level represents an increase of 100 per cent above the normal for the prepubertal child and is the exact normal level for the healthy woman of thirty years in a state of sexual rest. By reporting the deviation of the individuals from their personal norm in terms of per cent, data are secured which are comparable to each other. In presenting the results of this test (*i. e.*, percentage deviation from the norm), this convention has been adopted. While the male standard remains unchanged through life, the same convention has been followed for the sake of uniformity. In discussing the results obtained, it may not be out of place to repeat that as they are derived from individuals showing wide degrees of variation in functional level, the average values are much less than the deviation shown by individual cases in the series. Mild and severe conditions, with the several intermediate gradations, manifest themselves quantitatively through the amount of their variations from the standard. The

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\* \* The differences are undoubtedly gradual and progressive. In applying the test, it has been found to be practical to vary the several test doses by 10-gram amounts, and this convention defines the figures as given.

method of averages lessens the apparent magnitudes, leaving the expressed tendencies significant in sense and degree. In tests of this character the dysfunctional group, which is made up of mutually compensating units, tends toward a misleading normality. In the effort to minimize these hampering conditions as far as possible presentation is made with the same detail as that employed in the preceding table. The galactose tolerance data are given in Table XIII.

### NOTES

- A. A few cases have been omitted from the tabulation as a concomitant non-endocrine disease influencing sugar tolerance makes them mask the true picture.
1. One hypothyroid patient (male) at 60 gms. had an advanced chronic interstitial nephritis, and one at 20 gms a demonstrated liver involvement.
  2. Four hypothyroid patients (female) with demonstrated liver disorder average —68%.
  3. Two male castrates at 40 gms. had late chronic interstitial nephritis.
  4. Four hypogonad patients (female), averaging —80%, had severally cases of central nervous lesions (2), syphilis (1), and liver disorder (1).
  5. Three hypogonad patients (female), showing a normal post-menopause tolerance of 30 gms., all had an established nephritis and were over 60 years old.
  6. One hypoadrenal patient (female), with raised tolerance (+25%), had a long established chronic interstitial nephritis.
- B. In the pluriglandular cases, 20 gms. is taken as the demonstrated normal tolerance for the castrated female.

In the hypofunctional group failure of the pituitary uniformly produces an increase in tolerance of very marked proportions. With failure of the thyroid the same direction is observed, but both the amount of the increase and the frequency of its appearance fall far short of the pituitary influence. With the testicular failure no change is observed, while with the hypovarian patients there is uniformly a depression of the tolerance which in the average falls just short of 50 per cent. It is to be remembered that the group herein reported, however, contains only females in whom the menstrual function had been established; in the other words, with sugar tolerances above the pre-pubertal level. Hypoadrenalism, like gonad failure, seemingly causes a downward tendency and one of even more definite proportions than in the ovarian cases. This observation is at variance with all other reports recorded in the literature and has already been noted in connection with the exhibition of glycosuria

TABLE XIII  
GALACTOSE TOLERANCE

Observation	Endocrine										Not End.
	Hypo-functional					Dys-functional				Hyper- func- tional	
	Pit.	Thy.	Gon.	Adr.	Pl. Gl.	Pit.	Thy.	Pl. Gl.	Uncl.	Pit.	
Male--											
High (gms.).....	70	40	30	30	—	50	30	—	30	20	40
Low (gms.).....	40	30	30	20	—	5	20	—	10	5	10
% above normal.....	100	14	0	0	—	4	0	—	0	0	5
% dose variation above normal (Av.).....	+73	+33	0	0	—	+50	0	—	—	—	+33
% =normal.....	0	86	100	67	—	12	33	—	33	0	41
% below normal.....	0	0	0	33	—	84	67	—	67	100	54
% dose variation below normal (Av.).....	—	—	—	-33	—	-50	-33	—	-50	-53	-40
Female--											
High (gms.).....	120	60	30	40	50	80	40	60	40	20	40
Low (gms.).....	40	30	20	5	20	5	20	5	20	20	5
% above normal.....	100	38	0	0	50	7	0	15	0	0	0
% dose variation above normal (Av.).....	+72	+29	—	—	+100	+85	—	+75	—	—	—
% =normal.....	0	62	0	17	25	1	70	15	11	0	42
% below normal.....	0	0	100	83	25	92	30	70	89	100	58
%dose variation below normal (Av.).....	—	—	-45	-52	-25	-52	-25	-6	-35	-50	-39
Summary											
% above normal.....	100	32	0	0	50	6	0	15	0	0	2
% =normal.....	0	68	*100	33	25	5	56	15	17	0	41
% below normal.....	0	0	†100	67	25	89	44	70	83	100	57

\* Male. † Female.

in some of these cases. The fact only is recorded here and will be discussed more appropriately in a later paper. The pluriglandular cases exhibit the result of summation of the several diverse agents comprehended in the group.

The data in the dysfunctional group include only the pituitary, thyroid, and the pluriglandular cases. The transition influence is manifested with the pituitary, a few of the cases having been examined at a time when they were passing through the zone of normality. A persistence of an earlier overactivity is shown by the thyroid group with 44 per cent of the cases exhibiting a lowered tolerance. In the pluriglandular group the ovarian element is more in evidence than in the hypofunctional fraction in which pituitary failure dominated the series.

It is to be regretted that hyperthyroid cases do not appear in this summary. As was stated earlier, this condition does not ordinarily require so elaborate an investigation for the establishment of a diagnosis. The sugar test requires three days, and when a diagnosis could be made by a morning's study, co-operation was not obtainable for this time-consuming addition. Since this series was completed a few hyperthyroid cases have been given the sugar test. They confirm, in the main, the inference to be drawn from the two groups here presented, namely, a moderate lowering of the tolerance. Lowered tolerance with cases showing overactivity is seemingly of more frequent occurrence than is the converse in thyroid failure. A warrantable inference from this fact would be of the possible production by the thyroid of a second hormone acting on carbohydrate metabolism as thyroxin—or something related to it—may be regarded as regulating the energy metabolism. The hyperpituitary cases exhibit a strait antithesis of those showing failure. The practical abolition of any tolerance for galactose is the common finding in severe cases of overfunction.

A word in passing may be offered on the frequent association in the literature of pituitary disease with diabetes. That it is in some measure an outgrowth of the untrammelled speculations of the Viennese school admits no doubt, but it is perpetrated by several writers who patently do not subscribe to the theory of an interlocking glandular directorate. If the lowered tolerance of the acromegalic is but an expression of direct inhibition of the function of the islands of Langerhans, then consistently,



in hypofunction of the former the increased sugar tolerance must signify an augmented production of insulin or lessened inhibition of its activity. In one of our cases, not reported in this series, the galactose tolerance was 300 per cent above the normal. This should imply at least an equal increase in available insulin, the sequel of which would but ill accord with the typical pituitary obesity and the normal blood sugars. Many other arguments are adducible, but they may be left more fittingly, to later discussion. That influence on carbohydrate metabolism is not confined to the endocrine group is apparent from the table. Lowered tolerances predominate—the few high values being seen in advanced nephritis. In the group characterized by a lessened power of assimilation are found cases presenting various lesions of the central nervous system, syphilis, primary anaemia, liver disorders, malignant neoplasm, and psychoneuroses. The wisdom of excluding such fairly frequent disease conditions before interpreting a sugar test in terms of endocrine disorder should not require comment.

Before leaving this portion of the work, certain correlations may prove of value. In presenting them not only will the summaries already presented be considered, but, equally, individual cases representing extreme conditions. These latter must take first place, as in them one finds the extreme limits defined, and hence the functional tendencies illustrated most clearly. Equally, it must be borne in mind that in selecting the extreme case many features may present that in early and intermediate states do not occur in really significant magnitude. Such presentation, therefore, must be used with due caution when applied to the individual case.

TABLE XIV  
PHYSICAL MEASUREMENTS  
*Influence of Hypofunction*

	Pituitary	Thyroid	Gonad	Adrenal
Height .....	— — —	— — —	(+ +)	?
Sitting Height Index	— —	+ +	— —	?
Weight .....	+ + +	+ +	+ +	—
Lung Volume.....	—	— — —	—	—

To allow compact form, the data will be reduced to tables. In the interest of simplicity only hypofunctional tendencies will be listed, as the known and established hyperfunctional condi-

tions present in the main antitheses to the former. Dysfunctional states present too many permutations of the extreme types to be easily presentable. Records from the literature, not observed in this series, are enclosed in brackets.

Pituitary and thyroid dwarfism are coupled with the overgrowth of the long bones said to occur from castration in childhood (males only). A clear-cut adrenal influence has not been defined. The values for the sitting height index are probable but not certain. The weight relation seems fairly well established and that of the lung volume definitely so.

The urine values are insusceptible to this form of analysis. The urines in pituitary and gonad cases tend toward the normal, those with thyroid disease simulate, and those with adrenal malfunction define the picture of nephritis. This adrenal tendency is well marked in the urea curve. In the nitrogen partition the thyroid and adrenal cases show the greatest tendency toward high residual fractions and absolutely high values as well. The pituitary influence is indeterminate, the gonad picture tends toward normal.

The high blood uric acid of the pituitary cases, and high residual nitrogen and low blood sugar of adrenal disease, are the outstanding features of this group of analyses.

The general low white count and lymphocytosis, the latter most marked in adrenal, though frequently assuming high values in thyroid cases, and the eosinophilia of the pituitary and adrenal cases, are the most salient features of the blood morphology.

The accessory physical measurements incident to the respiratory metabolism may be presented in tabular form.

TABLE XV  
PHYSICAL FUNCTION

*Influence of Hypofunction*

Datum	Pituitary	Thyroid	Gonad*	Adrenal
Temperature .....	—	— —	0	0
Pulse .....	—	— — —	0 or +	0
Respiration .....	0	— —	0 or +	0
Blood Pressure.....	—	— —	— —	— — —
Alveolar CO <sub>2</sub> .....	0	0 or —	— — —	0 or —

\* Ovary only. The loss of the testicles in adult years lowers blood pressure and pulse rate slightly, but seemingly does not produce any marked effect in man.

The average pituitary case shows a generally normal trend, the thyroid a depression varying only in amount, ovarian failure produces a marked drop in blood pressure and a unique depression of alveolar carbon dioxide, while hypofunction of the adrenal exhibits a significant departure from normal only in its extremely low blood pressures.

As a point of differential significance the joint consideration of basal rate and sugar tolerance shows both qualitative and quantitative relations which are highly informative.

TABLE XVI

COMPARISON OF OXYGEN AND CARBOHYDRATE METABOLISM

*Influence of Hypofunction*

Datum	Pituitary	Thyroid	Gonad	Adrenal
Basal Rate.....	— — —	— — —	— — —	— — —
Galactose Tolerance.	+ + +	+ — —	— — —	— — —

Of the gonads only the ovary again is considered. Ablation of the testicles in adult years produces but a slight drop in the basal rate and no change in sugar tolerance. The differential features of the above scarcely require comment. One condition is frequently met that cannot be resolved by the above relationship. Many women are seen who show a basal rate of from —15 per cent to —20 per cent, and a sugar tolerance of 20 grams. These data could be due either to primary hypogonadism or to the common type of pituitary dysfunction with the anterior lobe under-, and the posterior, over-active. The remainder of the laboratory and clinical picture is absolutely essential to resolve the problem, the initial outcome many times being to establish no more than a greater probability for one or the other diagnosis.

With the foregoing expository statement concerning those tests whose character permits in some measure this form of presentation, attention may next be given to the group of special examinations.

In the main, these are chiefly serviceable as indicating the presence or absence of a non-endocrine disease state to which both the patient's presenting symptoms, as well as the results of certain of the laboratory tests, might be attributable. Exceptionally, such examinations may give positive evidences of endocrine significance, and to these the following discussion will be

limited. Before taking up details, however, a brief review of the extent of the special examinations may be presented in tabular form.

TABLE XVII  
SPECIAL EXAMINATIONS

Examination	Cases Examined	Positive Findings	
		No.	%
Eye .....	596	460	87
Ear .....	206	60	29
Barany .....	100	25	25
Audiogram .....	121	111	92
Nose and Throat.....	40	23	58
Heart (1).....	26	14	54
Pelvic .....	161	54	34
Cystoscopic .....	14	7	50
Orthopedic .....	13	12	92
Neurological .....	310	169	55
Skin .....	20	20	100
Endermal .....	47	25	53
Biopsy .....	6	4	67
Sputum .....	15	3	20
Duodenal Function.....	8	3	38
X-Ray (General) (2).....	633	362	58
X-Ray (G. I. Series) (3).....	30	14	47
Miscellaneous .....	240	..	..
<hr/> Total.....		2586	

(1) An electrocardiograph was not available at the time this series was completed.

(2) Each of these cases had a series of x-ray plates. Pictures of sella, sinuses, and thyroid were always secured and frequently chest, measured heart, and other plates were added.

(3) The Graham test had not been described at the time this series was completed.

It will be seen from the above tabulation that the average of special examinations for each case falls between 2 and 3. Since this series was completed additions to the staff, together with increase in equipment and inclusion of new methods, has augmented this phase of the work. At the present time the long

form cases average 8+ and the short form studies 5+ consultations.

The special examinations yielding positive information as to endocrine status may be taken up seriatim.

1. *Liver Function*: These studies—and more significantly the later investigations which have profited greatly through the application of new methods, the products of this and other research institutions—have demonstrated a frequent incidence of liver dysfunction in thyroid failure. There is not necessarily an earlier history of icterus nor of symptoms pointing to liver or gall bladder disease. The Graham test (44), icteric index (45), van den Bergh reactions (46), and more especially the elaborate methods based upon the examination of the duodenal contents which have been devised by McClure (47), give many channels of approach for the resolution of this problem. Such a liver condition may mask the otherwise clear-cut evidences of thyroid disease (modified sugar tolerance, atypical blood picture), and render a diagnosis uncertain. The condition is usually functional in character and frequently yields to duodenal lavage. Migraine of hepatic origin is frequently a concomitant picture.

2. *Ophthalmological Examination*: The production of ocular disturbance by pituitary tumors has been frequently recorded [Josefson (48), Cushing and Walker (49), de Schweinitz (50)], and even through temporary enlargements, as in pregnancy [Erdheim and Stumme (51), Carvill (52)]. Others have recorded changes even when no tumor growth could be demonstrated, and Oppenheim (53) has suggested the existence of a circulating toxic substance derived from the gland and producing optic nerve degeneration. As reported by Rowland (54), a yellow color of the discs, enlarged blind spots, and contraction of the form and color fields are frequently observed in pituitary disease in the absence of demonstrable tumor growth. One or more of these phenomena may also be found in thyroid and gonad involvements, though with less frequency than in the pituitary cases. That the general metabolic disturbance is a direct causal element is seemingly capable of demonstration. The pituitary, from its anatomical relationships, exercises influence through two channels, the others presumably through but one. Other

manifestations, such as cutting of the upper form fields and marked concentric contraction of the form and color fields have been recorded and are shortly to be discussed in the literature. Besides the direct endocrine indications, many evidences of non-endocrine disorders may be elicited in thorough eye examinations. In skilled hands the eye examination is probably more generally suggestive and informative than any other one special examination both in endocrine disease and in other non-endocrine localized or general derangements.

3. *Electrocardiogram*: It has been shown by Thacher and White (55) that thyroid failure may produce a more or less characteristic electrocardiographic picture; these findings have in part been substantiated in our clinic.\* An interesting feature is the restoration of the picture to the normal under thyroid medication (see later paper on the thyroid).

4. *X-Ray*: Aside from the large amount of information concerning non-endocrine conditions which this form of examination offers, there are potentially certain direct evidences which should be expected. Lack of epiphyseal union or premature closure are instructive and may support other evidences of aberrant growth relations of endocrine origin. Substernal thyroids may be shown by this means, and the information is of supplementary value.

Sella pictures are of value only when actual erosion of the clinoids or floor has taken place as the result of pronounced hyperplasia. In the great majority of pituitary cases, however, a normal sella is seen—if such a term be warranted to describe a bony structure so variable in its formation [see Camp (56)].

Equally, the diversity of outline of sellae enclosing wholly normal glands suggests caution in the establishment of a pituitary diagnosis on the evidence of a possible abnormal configuration of this structure alone. Thymus shadows, while possibly informative, lack specific indication. Aside from the lack of evidence of a true endocrine function of this gland, certainly in adult years, so-called persistent thymi are found to be far more frequent in necropsy reports than certain clinical writings would seem to indicate. They have been frequently observed in indi-

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\* Reid. Unpublished data. Personal communication.

viduals of adult and advanced years who have shown no other evidence of a status thymico-lymphaticus.\* It would seem equally plausible to regard a persistent thymus, in some cases at least, as but one evidence of a growth anomaly incident to an established endocrinopathy known to influence development. Further, it may be regarded as a resultant element in status lymphaticus rather than the causal factor.

One other finding under this caption requires brief comment. The inclusion of the pineal in the endocrine group is still open to question. Dandy's experiments (57) fail to show any real endocrine influence. Parenthetically it may be said that complete extirpation experiments that yield negative results are by far the most decisive; positive evidences may be produced by trauma to adjacent parts or to other agencies unassociated with the primary object of the experiment. In this series, 29 cases were reported with x-ray shadows interpreted as calcified pineal glands. The etiological classifications gave:

Not Endocrine.....	9
Pituitary Dysfunction.....	14
Pituitary Hypofunction.....	3
Gonad .....	2
Unclassified .....	1

In none of these cases was there demonstrable any stigmata which could be associated with the conventional evidences of pineal disease, nor did any of the histories contain suggestive records. It may be argued that all of the subjects were adults and that the pineal condition had probably occurred only after maturation. Such a position is tenable but equally if adopted leads to the inevitable corollary that in adult years, at least, the pineal has no striking endocrine function. While pituitary cases constitute over one-half of the group, it must be remembered that there were 270 of them who showed no pineal shadows—and that, further, many of the other patients did not have x-rays of the skull.

5. Such endocrine data as may be elicited by neurological, pelvic, and skin examinations are too well known to require elaboration in this report.

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\* Personal communication to me by Dr. George Burgess Magrath.

The many other observations listed are primarily important, as was stated above, in defining concrete disease conditions unassociated with the endocrine glands.

A few additional words may be permitted before bringing this first paper to its conclusion. The author wishes to emphasize that this can be at most but a preliminary communication. He may say with perfect candor that he is as acutely aware of the many shortcomings of this work as can be any of his readers. That it is the first formal presentation of investigations begun in 1912 is an earnest of good faith. What it embodies may be briefly stated. Certain objective criteria have been established for the determination of the presence of endocrine disease, and, further, its allocation to the individual gland at fault. Equally, it has been shown that a variety of non-endocrine conditions may simulate endocrine diseases both in some of their many clinical aspects, and equally in certain of the significant laboratory findings. In other words, for the establishment of the true etiology it is essential to conduct a general diagnostic study with the possible endocrine element determined only by exclusion. We have applied the method to the study of nearly 3,000 cases with results that seem to us encouraging, even while we recognize the limited amount of real knowledge yet available and the vast extent of the territories still unexplored. It is our hope that application of the correlations here presented may prove of some service to our colleagues in the resolution of their own problems. This independent application is essential to establish such worth as may lie in this method of approach.

Effort has been made to avoid controversy. Where the findings are at variance with conventional endocrine doctrine, the observed and tested facts upon which the conclusions rest are offered to speak for themselves. Many points of first importance must still be largely matters of interpretation, but at least objective data offer a firm foundation for a common starting point.

In conclusion, the writer wishes to pay his heartfelt tribute of thanks and appreciation to the many who have participated in this work. In the first place, thanks are due to those volunteers in the early days whose willing co-operation made the establishment of the normal standards possible; an even greater measure of appreciation is offered to those who in suffering and with disease heavy upon them gave a gracious and willing aid that



others might profit where they could not. Every tribute must be paid to the laboratory staff of the Evans Memorial, by whose skilled and patient hands the tens of thousands of exacting and delicate operations have been performed with consistent accuracy. And finally, a basic indebtedness is acknowledged to the group of friends, colleagues, and fellow workers, the full staff of the institution, whose generous assistance, highly skilled service and unfailing support and encouragement have made this work possible.

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NOTE.—In presenting the foregoing material no attempt has been made to embody a review of the existing literature. Individual citations pertinent to the thesis in hand have been included, but the huge volume of published work in this field makes even cursory notice far exceed the limits of publication. Excellent bibliographies are to be found in a number of works that have appeared in recent years, and to these reference is made for those who desire a more extended review of recent publications. Citations from the author's own work would be over numerous but for the fact that they are expository to the thesis in hand. The present paper is confined to describing a method and reporting certain results obtained with it. Conflicting views will be discussed at greater length in the later papers to which such material more properly belongs.

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# EXOPHTHALMIC GOITER AND MYXEDEMA: REPORT OF A CASE\*

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The characteristic phenomena of exophthalmic goiter are probably brought about because of the production and delivery to the tissues of an abnormal agent from the thyroid gland. This agent is usually associated with an excess of the normal thyroid secretion, but that it must be so is not essential to the hypothesis that in exophthalmic goiter two products are elaborated by the thyroid gland, nor is it consistent with theoretical or practical considerations of thyroid function and disease. There is abundant evidence that the thyroid gland may produce amounts of secretion sufficient to hold the basal metabolic rate at a normal level and still be associated with the phenomena of exophthalmic goiter, presumably because of an abnormal secretion. It is theoretically possible to have the abnormal thyroid secretion so limited in amount that, when controlled with compound solution of iodine (Lugol's solution) the patient shows frank evidence of myxedema; and in the same patient to find the phenomena of exophthalmic goiter when the patient is not taking iodine. This condition is exemplified in the following case:

A woman, aged twenty-eight, registered at the Mayo Clinic, September 13, 1924, complaining of protrusion of the right eye. Sixteen months previously she had become tired, nervous, and had lost 30 pounds in two months, in spite of a normal diet. Tonsillectomy was performed at that time, and following this she had gained strength and weight; the right eye, however, had become prominent. The nervousness disappeared and during the year before admission she had been intolerant of cold, had tired easily, and lacked energy.

General examination disclosed dry skin and moderate exophthalmos of the right eye. The thyroid gland was just pal-

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\* This case has been referred to by H. S. Plummer: The function of the thyroid gland. In the Beaumont Foundation Lectures, St. Louis, C. B. Mosby Company, 1926, 45-82.

pable. Measurement of the eyes with the exophthalmometer showed the right to be 20 mm., and the left 18 mm. The basal metabolic rates were  $-13$  and  $-16$  per cent. It was thought that the patient had had exophthalmic goiter with residual exophthalmos, and that the present symptoms were the result of a mild degree of hypothyroidism, or that the patient was one of those persons who normally have a low basal metabolic rate. The basal metabolic rate was elevated, and the patient was sent home with instructions to take 2 grains of desiccated thyroid daily, a dose which was holding the basal metabolic rate at  $-4$  per cent.

January 25, 1924, the patient returned. For the previous two weeks there had been loss of strength, increased sweating, and palpitation. She had lost 15 pounds in weight. The exophthalmos had remained unchanged, but stare was present. The right lobe of the thyroid measured 2 by 5 cm. and was very hard. There was frank evidence of hyperthyroidism. The basal metabolic rates were  $+49$  and  $+52$  per cent. The desiccated thyroid was discontinued, but there was no change in the basal metabolic rate after nine days. A diagnosis of exophthalmic goiter was made. The patient was then given ten drops of compound solution of iodine three times daily and in ten days the basal metabolic rate had dropped to  $+30$  per cent, the stare had disappeared, and the patient was improved. March 3, partial thyroidectomy was performed, leaving thyroid tissue amounting to half of the normal lobe on each side. The tissue removed weighed 62 gm. and the pathologic report was "hypertrophic parenchymatous thyroid." March 13, 1924, the patient felt well; the basal metabolic rate was  $+1$  per cent.

At the first observation there was no clinical evidence of myxedema; however, it is to be noted that the basal metabolic rate at that time was  $-16$  per cent and the edema of myxedema does not usually appear until the basal metabolic rate has dropped to  $-18$  or  $-20$  per cent. In view of the condition of the patient at the time of the second admission it was assumed that she had first come to the clinic in a state of complete remission from exophthalmic goiter. She was apparently a person whose basal metabolic rate is lower than the average normal. Exophthalmic goiter often develops in this type of case.

March 4, 1925, she returned for examination. She had been

in normal health until July, 1924, when she had again become nervous, had palpitation, and exophthalmos appeared in the left eye; that in the right eye had increased somewhat. In January, 1925, she had taken compound solution of iodine and had noted little change, except that there had been considerable intolerance to cold. At the present examination, moderate exophthalmos of both eyes was present, and there was edema of the lids of both eyes. The skin was cold. The facies was typically that of myxedema and there was bilateral exophthalmos. The basal metabolic rates were  $-28$  and  $-30$  per cent.

From the history it was clear that five months following thyroidectomy there had been a recurrence of exophthalmic goiter. This had been controlled with the iodine, and later the thyroid remnant had produced an insufficient quantity of its secretion to hold the basal metabolic rate at normal. It was anticipated at the time of this admission that stopping the iodine would allow the basal metabolic rate to rise and the characteristic evidences of exophthalmic goiter to appear. This opinion was based on Plummer's hypothesis that in exophthalmic goiter there is an active agent produced by the thyroid gland which causes the characteristic phenomena of this disease, and which is, presumably, an abnormal form of thyroxin. This abnormal agent is usually, but not necessarily, associated with excessive secretion of normal thyroxin. If, in this case, the phenomena of myxedema could be produced at will by the administration of iodine and by stopping it, these phenomena could be made to disappear and evidence of exophthalmic goiter substituted, we would then have proof of the coincident existence in this patient of both myxedema and exophthalmic goiter. Furthermore, almost incontrovertible evidence would be established in support of this hypothesis.

Compound solution of iodine, which had been taken continuously since January, was stopped and the basal metabolic rate rose, after sixteen days, to  $-14$  per cent. The patient then complained of nervousness; the intolerance to cold had disappeared. Edema of the eyelids diminished, and stare characteristic of exophthalmic goiter was present. Compound solution of iodine was again given and after eighteen days the basal metabolic rate had again dropped to  $-25$  per cent, with reappearance of the evidence of myxedema and loss of the stare and

nervous manifestations. Iodine was continued and desiccated thyroid was given; the basal metabolic rate rose to  $-2$  per cent. Evidence of myxedema disappeared and there was considerable improvement in the patient's symptoms.

In October, 1925, the patient returned. At this time she felt better than at any time since the onset of the illness. The exophthalmos had diminished and there was no edema of the lids. The basal metabolic rates were  $-7$  and  $-6$  per cent; the iodine was stopped and the desiccated thyroid continued in the same dosage. The basal metabolic rate rose in fourteen days to  $+6$  per cent, the patient became nervous and warmer, the eyes stared and puffiness of the lids of the type seen in exophthalmic goiter appeared. She was dismissed with instructions to take both compound solution of iodine and desiccated thyroid. A letter written October 7, 1926, stated that she had stopped all medication in February, 1926. The protrusion of the eyes remained the same. Since this time, she had noticed a slow pulse, and marked intolerance of cold. There were no nervous symptoms.

The response to iodine was exactly as anticipated, and, as is seen, relief from symptoms came only from the simultaneous administration of iodine and desiccated thyroid. There was, then, absolute deficiency of the thyroid secretion, and what secretion was present was partially of the character of that produced in exophthalmic goiter. Obviously, then, the cause of exophthalmic goiter was still active in the patient for some time following thyroidectomy, although when the abnormal agent of this disease was brought under control by compound solution of iodine, she became myxedematous. From the later correspondence it is apparent that the cause of exophthalmic goiter has since ceased to be active, but the thyroid deficiency persisted. Several cases have been seen in the clinic presenting the syndrome of exophthalmic goiter, and with basal metabolic rates from 0 to  $\pm 10$  per cent, dropping from  $-5$  to  $-15$  per cent after the administration of iodine. This case, however, is the only one observed in the clinic in which the basal metabolic rate was depressed because of the administration of iodine to so low a level as to be consistent, and coincident with the characteristic frank manifestations of myxedema.

# EPINEPHRINE SENSITIVENESS AT THE MENOPAUSE

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In a monograph recently published by myself (1), dealing with the causation and treatment of "flushing" at the menopause, and in a paper published in the British Medical Journal (2), I have drawn attention to certain phenomena associated with the administration of epinephrine to women at the menopause who complained of flushing. These were:

## FLUSHING PRODUCED BY EPINEPHRINE

Intravenous injections of 10 minims of a 1 in 1,000 solution of epinephrine hydrochloride in women complaining of flushing at the menopause gave rise, in all instances, to an immediate attack of flushing which was, in all respects, identical with those attacks which occurred spontaneously.

A consideration of the results obtained by observers, such as Petzetakis, on the effects of intravenous injections of epinephrine in normal individuals, yields no evidence of the production of flushing by this substance in such individuals. Control injections were given to my patients of the extract of the posterior portion of the pituitary body and of normal saline; no flushing, however, was produced by these injections.

Goetsch has shown that in some cases of hyperthyroidism the patients are remarkably sensitive to injections of epinephrine, and attacks of flushing have been frequently observed following the administration of epinephrine to such individuals.

Basal metabolic investigations were not performed in my cases, but no clinical signs of hyperthyroidism were present; furthermore, only those women were utilized for experimental work whose weight had remained constant or had increased since the onset of the menopause.

## EPINEPHRINE MYDRIASIS AT THE MENOPAUSE

Dixon has shown that instillation of epinephrine into the

conjunctival sac in normal individuals does not give rise to dilatation of the pupil.

Forty per cent of those women at the menopause complaining of severe flushing, whom I subjected to this test, showed dilatation of the pupil of transitory duration. The reaction was found to be constant on eight consecutive days in each instance.

Loewi has stated that epinephrine mydriasis may occur in cases of pancreatic diabetes. Bearing this in mind, therefore, an examination of the urine was undertaken where the pupil reaction to epinephrine occurred; in no instance, however, was evidence of glycosuria obtainable.

Since publishing these findings, I have extended my researches as follows:

#### INTRAVENOUS INJECTIONS OF EPINEPHRINE IN WOMEN AT THE MENOPAUSE NOT COMPLAINING OF FLUSHING

As was the position in my original experiments, the difficulty in obtaining clinical material was considerable. It was necessary to obtain patients who, after being fully informed of the unpleasant symptoms and the possible risk associated with the intravenous injection of epinephrine, were still willing to cooperate in the investigation required. Three volunteers only were forthcoming, and in these women I gave intravenous injections of 10 minims of epinephrine hydrochloride, diluted in 10 cc. normal saline. The injection was given extremely slowly. Immediately the injection was concluded, the pulse rate was found to be increased and the arterial tension raised (to the palpating finger).

With this increase in tension and pulse rate there occurred palpitation, headache, distress, and pallor of the face. This stage lasted between four and five minutes, and was identical with that which occurred following the intravenous injection of epinephrine in women at the menopause who complained of flushing. In the next stage, the headache and palpitation disappeared; the pulse rate fell to below normal level and was of low tension; some faintness was complained of. This stage, which I call the stage of reaction, lasted between four and five minutes. On comparing this stage with the one produced in those women at the menopause complaining of flushing, it would



seem that the stages in each group are identical with one exception; namely, the production of flushing. In other words, intravenous injections of epinephrine in women at the menopause produce flushing in the reactionary stage where this symptom has been complained of prior to the injection, and do not produce flushing where the menopause is not naturally associated with this symptom. In both groups the stage of reaction was quickly followed by a return of both the pulse rate and blood pressure to the normal level and the disappearance of all symptoms associated with the injection.

#### SUBCUTANEOUS INJECTIONS OF EPINEPHRINE

##### (a) *The Menopause associated with flushing*

A series of subcutaneous injections of .5 cc. epinephrine hydrochloride was given to 10 women at the menopause complaining of severe flushing; 10 women at the menopause not complaining of flushing, and 10 women having regular menstrual cycles.

The systolic blood-pressure and pulse rate were observed at five-minute intervals for 30 minutes. Subjective and objective symptoms were carefully noted and the conditions at the site of the injection closely observed. The maximum rise noted was coincident in time for both the blood-pressure and the pulse rate, and occurred in five minutes, 1 instance; in ten minutes, 6 instances; in fifteen minutes, 2 instances, and in twenty minutes, 1 instance.

The maximum increase in the systolic blood-pressure noted, in this series, was 25 mm. Hg.; the minimum, 12 mm. Hg. With the increase in blood-pressure there occurred an increase in the pulse rate of between 7 and 18 beats per minute. In all instances the blood-pressure and pulse rate had returned to the normal level within 30 minutes after giving the injection of epinephrine.

Palpitation was complained of by 6 women; throbbing in the head by 2, and 4 did not complain of any abnormal sensation. No flushing was observed in any instance.

In no case in this series were signs of hyperthyroidism present.

##### (b) *Menopause without flushing*

No change in the systolic blood-pressure or pulse rate above

5 mm. Hg., and 7 beats per minute, respectively, was observed; nor were there any subjective or objective disturbances associated with the injections in this series.

In 2 of the 10 women in this group increased sensitiveness to subcutaneous injections of epinephrine had been observed some weeks previously. Both of these patients had, at the time of the epinephrine sensitiveness, attacks of flushings; no increased sensitiveness was, however, observed on the occasion of these experiments when the flushings were not present.

(c) *Women with normal menstrual cycles*

No rise in the systolic blood-pressure or increase in the pulse rate above 8 mm. Hg., and 5 beats per minute, respectively, was noted in these women; subjective and objective symptoms were absent. The site of the injection showed, in all three groups, intense vaso-constriction immediately following the administration of epinephrine, which was still present, in lessened degree, at the end of 30 minutes.

FURTHER OBSERVATIONS ON EPINEPHRINE MYDRIASIS AT  
THE MENOPAUSE

*Technique:* Two drops of epinephrine hydrochloride were instilled into the conjunctival sac at 5-minute intervals, for 20 minutes. The reaction was considered to be positive if the pupil became obviously dilated, when compared with the untreated eye, within this time.

My material consisted of 32 women at the menopause complaining of flushing of varying intensity; 21 women at the menopause not complaining of flushing; 40 women with normal menstrual cycles.

(a) *Women at the Menopause complaining of flushing*

Of the thirty-two women in this group, only 2 gave pupil dilatation—namely, 6.2 per cent. In both of these patients, as in my original series, the mydriasis was noticeable 5 minutes after the instillation. The duration of the dilatation was 2 minutes in one instance, 3½ minutes in the other.

The urine was tested for glycosuria in both of these women. It will be noticed that, in this group, only 6.2 per cent gave an

epinephrine mydriatic reaction, as compared with 40 per cent in my original series.

It will be remembered that my original series consisted only of women suffering from severe flushing, whereas the group under consideration consists of women suffering from flushing of varying intensity. Furthermore, the 2 women in my latest series who gave an epinephrine mydriatic reaction, both complained of severe flushing. It would seem, therefore, that the intensity of the flushings has much to do with the incidence of epinephrine mydriasis at the menopause.

(b) *Women at the menopause not complaining of flushing*

No mydriasis was observed in this group.

Of the 21 women in this series, 5 had previously shown epinephrine mydriasis.

The positive pupil reaction was associated with attacks of flushing which had completely ceased at the time of the present experiment.

(c) *Women with normal menstrual cycles*

No mydriasis was observed in this series.

A consideration of these results justifies, I think, the following conclusions:

1. Women at the menopause who complain of flushing show an increased sensitiveness to epinephrine.
2. This increased sensitiveness is manifested as certain atypical phenomena associated with:
  - (a) Intravenous injections of epinephrine.
  - (b) Subcutaneous injections of epinephrine.
  - (c) Instillation of epinephrine into the conjunctival sac.
3. Whereas the atypical phenomena associated with the intravenous and subcutaneous injections of epinephrine are present in all cases of the menopause associated with flushing, epinephrine mydriasis is present only in cases complaining of severe flushing.
4. The atypical epinephrine phenomena do not occur in:
  - (a) Those women at the menopause who do not complain of flushing.

(b) Women whose menstrual cycles are normal.

5. Epinephrine sensitiveness at the menopause associated with flushing disappears when the attacks of flushing cease.

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# THYROXIN AS A DEPRESSANT OF CELL DIVISION; ITS EFFECT ON THE CLEAVAGE AND EARLY DEVELOPMENT OF SEA URCHIN AND ASCIDIAN\*

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Of the many studies of thyroid function that have appeared in recent years, relatively few have been concerned with the part played by the thyroid in differentiation. Fewer still have contributed observations on the influence of the thyroid on cell division. And among the latter, evidence of a direct effect on the dividing cell is almost entirely lacking.

Champy (1) described marked accelerations of cell division in certain regions of the frog tadpole following the addition of total thyroid to the aquarium water. Horning and Torrey (2,3) found that the barbule cells of the laced feathers characteristic of male domestic fowls are increased in number and their division accelerated by the addition of desiccated thyroid to the daily ration or the injection of thyroxin into the peritoneal cavity. In neither of these cases, however, is the effect due demonstrably to the direct action of the thyroid hormone on the cells concerned, uncomplicated by contributions from other tissues.

Ebeling (4) avoided such difficulties for the most part when he added living thyroid epithelium to pure cultures of chick fibroblasts and saw that the latter divided more rapidly than the controls. Carrel (5) had already found that the application of thyroid pulp to cutaneous wounds of the dog augmented the rate of cicatrization. But he found also that extracts of various tissues, of the Rous sarcoma, and of whole embryos, produced similar accelerations of the growth of connective tissue *in vitro*; and that no acceleration was produced by extracts that had been heated to 70 degrees or had been filtered through a Chamberland filter. Eberling's results, therefore,

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\*The observations recorded here were made at the Tortugas Laboratory of the Carnegie Institution of Washington, whose guest I was and for whose hospitality I am greatly indebted.

do not identify the activating substance or substances derived from the thyroid cells with the thyroid hormone; nor does Ebeling make any such assumption.

In sharp contrast with these effects of total thyroid when given to intact organisms or added to tissue cultures is the *depressing* effect which the crystalline thyroxin obtained from the thyroid has been observed to exert on the division rate of *Paramecium*, the magnitude of the effect varying with the concentration of thyroxin in the culture medium [Riddle and Torrey (6), Torrey (7); Torrey, Riddle and Brodie (8)]. Cori (9) concluded that thyroxin accelerates the division rate of *Paramecium*, though to a much smaller degree than thyroid extract. Woodruff and Swingle (10) were convinced by their experiments that "neither thyroxin (Squibb's) nor commercial desiccated thyroid, or fresh desiccated thyroid of the turtle produce any significant acceleration of the division rate of *Paramecium*." With this conclusion our own observations are in entire accord.

With thyroxin it is possible to obtain various reactions associated with thyroid activity and at the same time avoid some of the difficulties entailed by the use of the latter. By exposing protozoans like *Paramecium* to solutions of thyroxin, it is possible to bring the latter into direct contact with single cells, under conditions permitting direct observation. The bacteria forming the essential food supply of *Paramecium* introduce a source of error. This, we believe, was successfully controlled in our experiments. But was the reaction of *Paramecium* a special case?

To test this question, evidence has been sought in two directions, namely, from tissue cultures—modifying Ebeling's experiment by substituting thyroxin for living thyroid epithelium—and from the cleavage stages of suitable eggs. Preliminary results obtained by my assistant, Miss Hope Plymate, indicate that thyroxin depresses the division rate of chick fibroblasts *in vitro*. These observations, however, as yet unpublished, need confirmation. In a recent letter from which I quote with his permission, Dr. Carrel writes: "We never observed any acceleration in cell multiplication by using thyroxin in cultures of fibroblasts and other cells." Experiments during the past summer (1927) with the eggs of such widely divergent forms as the

sea urchin *Echinometra* and the ascidian *Phallusia* establish a similar conclusion on a broader foundation of evidence and suggest the probability that depression of division rate may be a characteristic effect of thyroxin on animal cells in general. This evidence will be given below in detail, along with evidence of depression of differentiation rate as well. In neither case does the effect appear to be referable directly to the iodine content of the thyroxin molecule.

*Echinometra lucunter* and *Phallusia nigra* are abundant at the Tortugas. Both were breeding in August. Eggs and sperm were discharged by *Echinometra* promptly in the laboratory. They were removed from the gonoducts of *Phallusia*. In both cases, fertilization was initiated within ten minutes of the laying or taking of the eggs. The latter were transferred in approximately equal numbers to finger bowls each containing 100 cc. of sea water to which thyroxin had been added in concentrations from 1 part in 50,000 to 1 part in 1,600,000. In both experimental and control bowls the initial pH of the water was approximately 8.4. The temperature varied about 5 degrees during the twenty-four hours and often reached 29-32 degrees C. during the warmest part of the day. These high temperatures tended to shorten the interval between successive cleavages and thus probably to obscure somewhat the thyroxin effect.

The solution of thyroxin was prepared by placing in a watch glass a few milligrams of the crystalline product furnished by E. R. Squibb and Sons, adding 2 to 4 drops of N/10 NaOH—in which it dissolved—transferring this by pipette to a few centimeters of rain water containing a drop or two of N/10 NaOH and mixing this with the amount of sea water necessary to make the dilution required. In the first few experiments the controls were made up with rain water and NaOH to duplicate in these respects the thyroxin solutions. Later, these precautions were found to be unnecessary and were discontinued.

To obtain an accurate estimate of the effect of thyroxin on the division rate, continuous observations on given eggs in both experimental and control dishes possess obvious advantages. For several reasons, this method was not feasible in these experiments. Besides mechanical difficulties easily avoidable in another season, the failure of the eggs in one lot to cleave simultaneously was a source of embarrassment. The eggs often showed wide variations of cleavage from unsegmented eggs to the 64 cell stage in both thyroxin and control dishes.

Under the circumstances, the following method was used, which, though not ideal, was sufficiently precise to establish the essential facts. Samples of eggs were withdrawn with pipettes from one dish after another and examined in watch glasses or on slides. Experimental and control eggs were compared with reference to: the time at which the first cleavage occurred; the ratio of segmented to unsegmented eggs; the most advanced stage at a given time; the beginning of gastrulation; the activities and differentiation of the larvae. The last item obviously refers to the progress of differentiation and development rather than to the cleavage rates of the blastomeres. In some cases, hasty inspection was sufficient to establish the relative rates at which cleavage and development were taking place. In most cases, all the eggs in each sample drop were counted and classified with reference to the stage of cleavage they had reached. It was

thus clear for a given sample how many cells of the total number were unsegmented, how many were in the 2-cell stage, the 4-cell stage, and so on.

#### EXPERIMENTS WITH ECHINOMETRA LUCUNTER

The effect of thyroxin in a concentration of 1:50,000 is typically displayed in one of the early experiments. The eggs laid by a single female at 11:35 A. M. were fertilized immediately. Ten minutes later they were transferred to dishes containing thyroxin in a concentration of 1:50,000, and to control dishes. The progress of the experiment is recorded in the accompanying table which includes: several counts of both thyroxin (T) and control (C) eggs, with the number in each cleavage stage, and the per cent. in process of segmentation.

TABLE 1

Time		No. Eggs counted	No. 2-cell	No. 4-cell	No. 8-cell	% Segm.
Aug. 4	Lot					
12:40—1:03 p.m.	T	363	21	7	0	7.7
	C	406	28	14	0	10.3
1:07—1:27 p.m.	T	229	31	23	1	24.0
	C	251	33	25	2	23.9
1:30—1:54 p.m.	T	164	14	17	0	20.0
	C	256	19	60	10	34.7
Totals	T	756	66	47	1	15.0
	C	913	80	99	12	20.9

At 8:00 A. M., August 5, 25-40 per cent of the controls were swimming up. These swimming forms included spherical, ovate and angular larvae, the latter with skeletal spicules. In the thyroxin cultures, fewer than 1 per cent were moving. Some were swimming up. These included spherical and ovate forms. There were no angular forms. Most of the eggs were on the bottom disintegrating.

The eggs of another female were laid at 3:30 P. M. and fertilized five minutes later. At 5:30 P. M., repeated sampling showed that less than 20 per cent of the thyroxin eggs had segmented while all of the controls had done so. By 6:30 P. M., many of the latter had become blastulae; but there was no comparable development of the thyroxin eggs which were already showing certain cortical abnormalities and had begun to disintegrate by the following morning.

These results are typical. It appears, therefore, that *thyroxin in a concentration of 1:50,000 completely inhibits the cleavage of the majority of the eggs of Echinometra and hastens their disintegration, that it retards the cleavage and embryonic development of others which go on to gastrulation, and that it does not accelerate the cleavage of any of them.*

*Thyroxin in a concentration of 1:75,000 produces similar though somewhat less marked results.* More eggs segment, and disintegration is farther deferred. Those eggs that do segment, however, do so more deliberately than the controls and develop as far as gastrulation more slowly. In one lot of eggs, on the



morning following fertilization, many were found on the bottom unable wholly to free themselves from their membranes. Constricted into irregular dumbbell forms for the most part, they continued to differentiate for a time, developing skeletal spicules but failing to become normal larvae.

This abnormality occurred only twice in my experiments, in both cases in solutions of thyroxin made up from the same vial of crystals. It was noted at the time that this lot of thyroxin dissolved less readily than was customary, which further suggested a departure from standard that was probably responsible for the abnormal eggs.

*In thyroxin at a concentration of 1:100,000, six lots of eggs from six different females gave similar results.* The essential facts as observed in three of them are recorded in Tables 2, 3 and 4. The other lots add nothing of pertinent interest.

TABLE 2  
EGGS LAID AND FERTILIZED AT 10:45 A. M.

Time	Thyroxin			
	1:100,000	1:200,000	1:400,000	Control
11:43 a. m.				Among 80 4 2c
11:48	No 2c	2c seen		
11:53			Among 475 30 segm	Among 144 32 segm
12:05 p. m.		Among 142 32 2c 1 4c		Among 64 24 2c 4 4c
12:10	Among 255 7 2c 2 4c			
12:15		Among 100 38 2c 4 4c		Among 120 103 2 and 4c
12:30			No 8c	Several 8c
12:35		2 8c		
12:40	Among 100 4 2c 0 4c			Among 123 20 2c 70 4c 4 8c
1:05	0 16c	0 16c	1 16c	Several 16c
2:15	Mostly unseg. few 4 and 8 c	Many 16c few 32c	Largely 16 and 32c	Spherical blastulae

TABLE 3  
EGGS LAID AND FERTILIZED AT 11:00 A. M.

Time	Thyroxin			
	1:100,000(T <sub>1</sub> )	1:200,000(T <sub>2</sub> )	1:400,000(T <sub>3</sub> )	Control (C)
11:55 a. m.	Among 75 11 2c			Among 60 50 2c
12:05 p. m.		Among 81 19 2c 2 4c	Like C	Among 85 71 2c 1 4c
12:09	Among 75 53 2c 2 1c			
12:20	Among 100 11 1c			Among 85 20 1c 1 8c
12:25		1 8c		
1:00	Many 2, 4, 8c few 16c			Among 100 60 8c 31 16c
1:30	Behind C	16c, 32c	16c, 32c	Like T <sub>2</sub> , T <sub>3</sub>
4:50	Not swimming large cells	Swimming, behind C	?	Swimming
8:30	Swimming, spherical	Like C	Like C	Actively swimming, elongated
9:00 a. m.	Gastrulae, not angular	Not angular	More advanced than T <sub>2</sub> , less than C	Angular, compressed

TABLE 4  
EGGS LAID 12:30 P. M.; FERTILIZED 12:40 P. M.

Time	Thyroxin			
	1:100,000(T <sub>1</sub> )	1:150,000(T <sub>2</sub> )	1:300,000(T <sub>3</sub> )	Control
1:50 p. m.	2c, 4c present	2c, 4c present	2c, 1c present	2c, 4c present
2:30	Among 100 20 4c fewer 8c than in C			Among 100 50 4c more 8c than in T <sub>1</sub>
2:40		Occasional 16c	Like C	More 8 and 16c than in T <sub>2</sub>
3:20	2, 4, 8, 16c occasional 32c			Among 100 50 32c
3:40		Behind C	Behind C	
8:00	Not swimming	Not swimming	Swimming spherical ovate	Much larger prop. larvae swimming
8:00 a. m.	Spherical inactive	Like T <sub>1</sub>	Ovate and helmet sh.	Flattened angular advanced over T <sub>3</sub>

*Thyroxin in a concentration of 1:133,000 produced comparable results, in two lots of eggs.* In the first, eggs laid and fertilized at 10:00 A. M. were transferred to thyroxin at 10:40 A. M. By 1:00 P. M. several eggs had reached 16- and 32-cell stages in the control dishes, while none had passed beyond the 8-cell stage in thyroxin. On the following morning, the eggs in thyroxin were apparently in good condition, but distinctly behind the controls in development. In the second, eggs laid at 10:30 A. M. fertilized at 10:40 A. M. and transferred to thyroxin at 11:15 A. M. had not reached the 16-cell stage by 1:00 P. M., although the controls had. At 3:15 P. M., this lag was further apparent in the distinctly lower average cleavage of the former. On the following morning, both thyroxin and control eggs were swimming abundantly; but the former were spherical, the latter helmeted and angular.

*Thyroxin in a concentration of 1:150,000 produced similar results in two other lots of eggs, notes regarding one of them being recorded in Table 4.* The eggs of the other lot were laid and fertilized at 2:10 P. M. At 3:27 P. M., among 50 thyroxin eggs, 10 were in the 2-cell stage, 1 in the 4-cell stage; among 78 control eggs, 13 were in the 2-cell stage, 5 in the 4-cell stage, and 2 in the 8-cell stage. By 4:30 P. M., 16- and 32-cell stages had appeared among the thyroxin eggs, but were fewer in number and less regular and compact than in the controls. On the following morning, there were gastrulae among both thyroxin and control eggs, but the latter were more advanced.

*Thyroxin in a concentration of 1:200,000 was given to five lots of eggs.* Its retarding effect on cleavage in two of these is early apparent in Tables 2 and 3. In a third lot, abnormalities occurred to which reference has already been made as having been due probably to an impurity or variation in the thyroxin itself. In the other lots, there was no retardation of early cleavage, it being apparent only after 4 to 5 hours. Otherwise, the eggs of all lots reacted similarly.

*Thyroxin in a concentration of 1:300,000 was given to three lots of eggs.* Its retarding effect is still apparent, but less pronounced. One lot of eggs is recorded in Table 4. Another, laid and fertilized at 10:00 A. M. and transferred to thyroxin at 10:15 A. M. showed, at 12:45 P. M. in a sample of 20 eggs, 5 in the 2-cell stage and 4 in the 4-cell stage; while in a sample of 24 eggs from the control, 21 were in the 4- (or 8-) cell stage. Both thyroxin and control eggs were cleaving well at 2:50 P. M., many in the 64-cell stage being present in each group. At 10:15 A. M. of the following day, both were swimming up abundantly and apparently in excellent condition. The thyroxin eggs had now become rounded and also angular larval forms; but they were less advanced than the controls, there being more angular forms and a greater differentiation of these among the latter. Twenty-four hours later, the thyroxin eggs were still behind the controls. On the following morning, the former were dead, the latter in good condition. In the third lot of eggs, laid and fertilized at 1:45 P. M. (with sperm that had been discharged an hour before), there was little to choose between thyroxin eggs and controls at 3:30 p. m. Both were cleaving abundantly. There were traces of irregularity in the cleavage of the former, but no lag. By the next morning, however, though a cloud of healthy larvae was afloat in both thyroxin and control dishes, the former contained relatively very few angular forms, the latter many and characteristically flattened.

Of the four lots of eggs exposed to thyroxin in a concentration of 1:400,000, two appear in Tables 2 and 3. The other lots tell essentially the same story. In one of them there was a lag in cleavage among the thyroxin eggs similar to what may be noted in Table 2. In the other, no lag was recognized. On the following morning, in both lots, many eggs had become young plutei, with shorter arms in the thyroxin cultures than in the controls.

A single lot of eggs was treated with thyroxin in a concentration of 1:600,000. During the first day, no differences were noted between thyroxin and control eggs. On the following morning, the controls were again in the lead.

This completes our observations on the effect of thyroxin on sea urchin eggs. The data may be summarized by saying that while they provide no evidence for an accelerating effect of thyroxin on either the cleavage or the differentiation of these eggs, they do support the conclusion that in the concentrations used, thyroxin depresses the processes of both differentiation and division, to a degree varying with the concentration.

The mechanism of this effect is not clear. That the iodine of the thyroxin molecule is not the essential factor seems probable from the following observations on the effects of potassium iodide in much higher concentrations. In a concentration of 1:42,750 KI, which represents, in terms of iodine, a thyroxin solution of 1:50,000, *Echinometra* eggs kept step with the controls, cleaving as early and as rapidly and being as far advanced at the end of 24 hours, and living as long.

Eggs raised in 1:855 KI developed almost as satisfactorily, remaining practically abreast of the controls for 8 hours, swimming up vigorously as helmet forms at the end of 24 hours, and living for another 24 hours, developing in the meantime skeletal spicules—but no arms. The controls at that time were well developed plutei.

Eggs raised in 1:300 KI equalled the controls for 4 hours after fertilization. Three hours later, they resembled the controls in form but were less active.

#### EXPERIMENTS WITH THE EGGS OF PHALLUSIA NIGRA

In Table 5 are summarized the observations on a mixed lot of eggs taken from the oviducts of six individuals, fertilized by sperm

from two others at 11:27 A. M., and distributed at 11:35 A. M. to 4 dishes containing thyroxin in concentrations running from 1:50,000 to 1:200,000 ( $T_1$ - $T_4$ ), and one control dish (C). The figures in each column refer to the number and cleavage stage of all eggs found by inspection of sample drops to be in cleavage at the time specified. In three cases only, total counts are indicated. Such figures do not provide an adequate picture of relative proportions, but they are not without value in this connection. It should be remembered, further, that the time at which a cleavage stage was first observed is not necessarily the time at which the cleavage occurred.

The outstanding facts in this table are:

1. The small number of eggs segmenting in thyroxin. Not more than 5 per cent had segmented in any of the dishes 2.5 hours after fertilization, as against 85 per cent in the controls.

2. The lag in the cleavage of the eggs in 1:500,000 thyroxin.

TABLE 5

Time	Thyroxin				
	$T_1$ 1:500,000	$T_2$ 1:100,000	$T_3$ 1:150,000	$T_4$ 1:200,000	Control
11:44 a. m.	0				
12:15 p. m.		In 50, 2 8c			
12:20				1 4c, 1 8c	Sev. 2 and 4c 2 8c
12:27-30	1 4c	1 8-16c	1 2c, 1 4c 1 16c		2 2c, 1 4c 1 8c, 1 16c
12:35				1 16c	
12:40	1 8-16c				
12:45-50		1 2c, 2 4c, 1 8c	1 4c, 2 16c, 1 32c		Numerous 2c sev. 4c, 8c, 16c, 3 32c
1:00-08			In 100, 1 8c, 2 32c		In 100, 9 2c, 7 4c, 5 8c, 1 16c, 1 32c
1:20	No more seg.	No more seg.	No more seg.	No more seg.	
1:55	No more seg.	No more seg.	No more seg.	No more seg.	In 100, 88 seg.

The events of the first two hours of another experiment are summarized in Table 6. The eggs were taken from 10 animals, mixed and fertilized by sperm from 4 others at 11:27 A. M. and then transferred to experimental and control dishes. The former contained thyroxin in concentrations of 1:200,000 ( $T_1$ ), 1:300,000 ( $T_2$ ), 1:400,000 ( $T_3$ ), 1:500,000 ( $T_4$ ), 1:600,000 ( $T_5$ ), 1:800,000 ( $T_6$ ), 1:1,000,000 ( $T_7$ ), 1:1,200,000 ( $T_8$ ), 1:1,600,000 ( $T_9$ ), 1:2,000,000 ( $T_{10}$ ).



The farther history of this experiment follows:

$T_1$  (1:200,000)

- 1:30 p.m. 11 of 104 eggs cleaving: 2 2c, 1 4c, 3 8c, 2 16c, 3 32c.  
 2:35 12 of 79 eggs cleaving.  
 3:40 As at last reading.  
 4:50 A few larvae; many undivided eggs, as before.  
 6:45 Larvae farther advanced; otherwise as before.

$T_2$  (1:300,000)

- 1:36 p.m. 19 of 95 eggs cleaving: 7 2c, 5 4c, 3 16c, 3 32c, 1 64c.  
 2:35 27 of 37 eggs cleaving.  
 3:40 50 of 58 eggs cleaving.  
 4:50 Farther advanced than  $T_1$ ; many more larvae.

$T_3$  (1:400,000)

- 1:41 p.m. 29 of 66 eggs cleaving: 4 2c, 12 4c, 2 8c, 5 16c, 4 32c, 2 64c.  
 2:35 50 of 59 eggs cleaving.  
 3:40 50 of 55 eggs cleaving.  
 4:50 Larvae more advanced than in  $T_2$ .

$T_4$  (1:500,000)

- 1:47 p.m. 44 of 78 eggs cleaving: 6 2c, 6 4c, 5 8c, 11 16c, 15 32c, 1 64c.  
 2:45 99 of 104 eggs cleaving.  
 3:40 56 of 60 eggs cleaving.  
 4:50 Larvae with longer tails than in  $T_1$ - $T_3$ ; as in C.

$T_5$  (1:600,000)

- 1:53 p.m. 34 of 72 eggs cleaving: 10 2c, 6 4c, 4 8c, 7 16c, 7 32c.  
 2:45 95 of 100 eggs cleaving.

$T_6$  (1:800,000)

- 2:00 p.m. 42 of 63 eggs cleaving: 4 2c, 7 4c, 7 8c, 10 16c, 12 32c, 2 64c.  
 2:45 50 of 55 eggs cleaving.  
 3:40 Not distinguishable from C.

$T_7$  (1:1,000,000)

- 2:30 p.m. 95 of 100 eggs cleaving: all stages.  
 4:50 As in C.

$T_8$  (1:1,200,000)

- 2:30 p.m. 100 of 100 eggs cleaving: all stages.  
 4:50 As in C.

$T_9$  (1:1,600,000)

- 2:19 p.m. 49 of 68 eggs cleaving: 8 2c, 2 4c, 4 8c, 6 16c, 7 32c, 12 64c.  
 10 gastrulae.  
 2:55 97 of 100 eggs cleaving.  
 4:50 As in C.

$T_{10}$  (1:2,000,000)

- 2:15 p.m. 15 of 27 eggs cleaving: 3 2c, 2 4c, 2 8c, 1 16c, 2 32c, 1 64c,  
 4 gastrulae.  
 2:53 100 of 100 eggs cleaving.  
 4:50 As in C.

C

- 2:06 p.m. 53 of 82 eggs cleaving: 14 2c, 8 4c, 3 8c, 3 16c, 4 32c,  
 1 64c, 20 gastrulae.  
 2:51 59 of 61 eggs cleaving.  
 3:40 100 of 100 eggs cleaving.  
 4:50 Larvae as in  $T_1$ - $T_{10}$ .  
 6:45 A very few larvae have emerged.

It appears from these records that thyroxin in a concentration of 1:200,000 ( $T_1$ ), produced the following effects that set it rather apart from the rest: cleavage began later and involved fewer eggs, gastrulation occurred later, and the larvae present 5.5 hours after fertilization were inferior both in number and in development. The control (C) was distinguished by the largest proportion of cells involved in cleavage from the beginning; and was surpassed in no respect by any of the others. The latter, though very much alike, are divisible into two groups, the dividing line running between  $T_3$  and  $T_4$ . The first group, including  $T_2$  and  $T_3$ , was a bit retarded both as to rate of cleavage and the rapidity with which the maximum number of eggs to cleave was attained. As for the second, including  $T_1$ - $T_{10}$ , there was little to distinguish one lot of eggs from another except with reference to the last point. In a concentration, then, of 1:500,000 or more, thyroxin had little or no effect on the course of cleavage or development.

One more experiment will be considered. Eggs from eight animals were mixed and fertilized by sperm from four, at 11:00 A. M. In ten minutes, they were distributed to dishes containing concentrations of thyroxin varying from 1:200,000 to 1:1,000,000, and one control dish containing sea water only. The course of events in each dish as determined by means of sample drops will be given first, to be followed by tabulations and comment.

#### $T_1$ (1:200,000)

- 11:40 a.m. Among 50 eggs, 1 4-cell stage.
- 12:05 p.m. Among 47 eggs, 1 16-cell.
- 1:05 An occasional gastrula; no cleavage stages.
- 1:30 An occasional 64-cell stage or gastrula; many dead eggs.
- 3:00 Among 100 eggs, 10 have cleaved.
- 6:40 These are now larvae, still within egg membranes.

#### $T_2$ (1:250,000)

- 11:40 a.m. Among 50 eggs, 2 2-cell, 1 4-cell stage.
- 12:06 p.m. Among 33 eggs no cleavage stages.
- 1:07 As in  $T_1$ .
- 1:22 Among 52 eggs, 6 gastrulae.
- 3:00 Among 100 eggs, 15 have cleaved.
- 6:40 As in  $T_1$ .

#### $T_3$ (1:300,000)

- 11:48 a.m. Among 79 eggs, 1 2-cell, 2 4-cell stages.
- 12:07 p.m. Among 35 eggs, 1 8-cell, 2 16-cell.
- 1:09 As in  $T_1$ , with perhaps more gastrulae.
- 1:34 Among 53 eggs, 11 gastrulae.
- 3:00 Among 100 eggs, 12 have divided.
- 6:40 As in  $T_1$ .



T<sub>1</sub> (1:350,000)

- 11:44 a.m. Among 100 eggs, 2 2-cell, 4 4-cell.  
 12:08 p.m. Among 50 eggs, 1 2-cell, 1 4-cell, 1 8-cell, 3 16-cell.  
 1:11 16-, 32-, 64-cell and gastrulae present.  
 1:36 Among 34 eggs, 6 gastrulae.  
 3:00 Among 61 eggs, 13 have divided.  
 6:40 As in T<sub>1</sub>.

T<sub>2</sub> (1:400,000)

- 11:50 a.m. Among 48 eggs, 2 4-cell, 1 8-cell.  
 12:10 p.m. Among 47 eggs, 2 2-cell, 1 4-cell, 1 8-cell.  
 1:14 Among 35, 11 have cleaved: 2 to 64-cell stages.  
 1:37 15 of 51 eggs have cleaved; mostly gastrulae.  
 3:00 20 of 47 have cleaved.  
 6:40 Larvae, in advance of T<sub>1</sub>.

T<sub>3</sub> (1:450,000)

- 11:45 a.m. Among 100 eggs, 3 2-cell, 1 4-cell.  
 12:12 p.m. Among 59 eggs, 1 4-cell, 1 8-cell, 1 16-cell, 2 32-cell.  
 1:16 Among 70 eggs, 1 16-cell, 10 gastrulae.  
 1:40 12 of 39 have cleaved.  
 3:00 Larvae in egg membranes.  
 6:40 Larvae slightly in advance of T<sub>2</sub>.

T<sub>4</sub> (1:500,000)

- 12:04 p.m. Among 77 eggs, 1 2-cell, 1 4-cell, 1 8-cell, 1 16-cell.  
 12:21 Among 49 eggs, 4 2-cell, 3 4-cell.  
 1:19 Among 33 eggs, 13 have cleaved; mostly gastrulae.  
 1:42 22 of 33 eggs have cleaved; all stages.  
 3:00 50 of 100 eggs have cleaved.  
 6:40 Larvae slightly in advance of T<sub>3</sub>.

T<sub>5</sub> (1:600,000)

- 11:53 a.m. Among 54 eggs, 2 4-cell, 3 8-cell.  
 12:19 p.m. Among 66 eggs, 2 2-cell, 2 4-cell, 1 16-cell, 2 32-cell.  
 1:21 20 of 45 eggs have cleaved; various stages, including several gastrulae.  
 1:44 19 of 55 eggs have cleaved.  
 3:00 20 of 41 eggs have cleaved.  
 6:40 Larvae slightly in advance of T<sub>4</sub>.

T<sub>6</sub> (1:800,000)

- 11:56 a.m. Among 64 eggs, 2 8-cell.  
 12:23 p.m. Among 13 eggs, 1 32-cell.  
 1:23 18 of 31 eggs have cleaved; 9 gastrulae.  
 1:46 26 of 38 eggs have cleaved; all stages.  
 3:00 90 of 100 eggs have cleaved.  
 6:40 Larvae slightly in advance of T<sub>5</sub>.

T<sub>10</sub> (1:1,000,000)

- 11:58 a.m. Among 32 eggs, 6 2-cell, 2 4-cell, 1 8-cell.  
 1:25 p.m. 41 of 56 eggs have cleaved; all stages, many gastrulae.  
 1:48 26 of 34 eggs have cleaved; all stages.  
 3:00 75 of 85 eggs have cleaved.  
 6:40 Larvae a little ahead of T<sub>5</sub>-T<sub>6</sub>.

C	
11:44 a.m.	Among 100 eggs, several 2-cell, several 4-cell.
12:01 p.m.	Among 65 eggs, 10 2-cell, 2 4-cell, 2 8-cell, 3 16-cell.
12:14	Among 53 eggs, 10 2-cell, 9 4-cell, 3 8-cell, 2 16-cell, 3 32-cell.
1:27	38 of 43 eggs have cleaved; all stages, including many gastrulae.
1:50	91 of 100 eggs have cleaved.
3:00	100 of 100 eggs have cleaved.
6:40	Larvae as in T <sub>10</sub> .

These lots of eggs fall into two groups, defined by the amount of thyroxin in solution, by the number of eggs in process of cleavage at 3:00 P. M., and by the rate at which that maximum was attained.

In Group 1 are T<sub>1</sub>-T<sub>4</sub>, with thyroxin from 5.00 to 2.85 mgm. per L.  
In Group 2 are T<sub>5</sub>-T<sub>8</sub>, with thyroxin from 2.50 to 1.66 mgm. per L.  
In Group 3 are T<sub>9</sub>-T<sub>10</sub>, with thyroxin from 1.25 to 1.00 mgm. per L.  
In Group 4 is C.

Cleavage was observed as early in Groups 1-3 as in Group 4, not, however, in as many eggs. Succeeding stages appeared, also, about as early in Groups 1-3 as in Group 4, again, however, in smaller numbers. In Group 1, only 10-21 per cent of the eggs had cleaved by 3:00 P. M.; in Group 2, about 43 per cent had done so; in Group 3, 89 per cent; in Group 4, 100 per cent.

Table 7 indicates the progress of cleavage in all lots of eggs up to 3:00 P. M. The numerator of each fraction represents the number of eggs in cleavage in a given sample, the denominator the total number of eggs counted.

By 6:40 P. M., there were tailed embryos in all dishes. Those in T<sub>1</sub>-T<sub>4</sub> were in about the same stage of development, still within the egg membrane. Those in T<sub>5</sub>-T<sub>10</sub> were more advanced, progressing very gradually from T<sub>5</sub> to T<sub>10</sub>. C was clearly in the lead in that about 10 per cent of the larvae had emerged.

The foregoing data are the basis for the following conclusions:

1. Thyroxin affects the eggs of *Echinometra* and *Phallusia* similarly.

2. It accelerates neither cleavage rate nor the processes of differentiation.

TABLE 7

Time	T <sub>1</sub>	T <sub>2</sub>	T <sub>3</sub>	T <sub>4</sub>	T <sub>5</sub>	T <sub>6</sub>	T <sub>7</sub>	T <sub>8</sub>	T <sub>9</sub>	T <sub>10</sub>	Control
11:40-49	1/50	3/50	3/79	6/100		3/100					More 2 and 4c
11:50-59					3/48			5/54	2/64	9/32	
12:00-09	1/47		3/35	6/50							
12:10-19					4/47	5/59		7/66	1/13		26/53
12:20-29							7/49				
1:00-09	Few	See T <sub>1</sub>	See T <sub>1</sub>								
1:10-19				More than T <sub>3</sub>	11/35	11/70	13/33				
1:20-29								20/45	18/31	41/56	38/43
1:30-39		6/52	11/53	6/34	15/51						
1:40-49						12/39	22/44		26/38	26/34	91/100
3:00	10/100	15/100	12/100	13/61	20/47		50/100	20/41	90/100	75/85	100/100

3. On the contrary, it *retards* both cleavage rate and differentiation.

4. This effect varies in degree with the concentration of thyroxin.

5. It is not due primarily to the iodine in the thyroxin molecule.

6. Since thyroxin depresses cell division in such widely different organisms as *Paramecium*, *Echinometra* and *Phallusia*, it may well be that it is a depressant of cell division throughout the animal kingdom.

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# EFFECTS OF ULTRAVIOLET LIGHT ON PARATHYROIDECTOMIZED RATS

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The purpose of this paper is to report briefly some experiments on the effect of ultraviolet light upon thyroparathyroidectomized albino rats. Similar experiments have already been done by Swingle and Rhingold (1) upon the dog. The rat is in some ways a more convenient subject, and the general interest at the present time in the therapeutic application of ultraviolet light, as well as the possibility that such work might help to elucidate the physiology of the parathyroids, seemed to justify experiments on another variety of animal. However, the results here reported for the rat will be found to agree in general with those obtained for the dog.

In the preliminary experiments, the lack of sensitiveness of the rat to ultraviolet light became apparent. Through the cooperation of Miss Irene Smith of the Physiotherapy Department the author was enabled to use a number of mercury-vapor quartz lamps which are routinely used in the treatment of Dispensary patients. For these lamps, at a skin distance of 40 inches, an initial exposure of 3 minutes suffices to produce a marked erythema in the unhabituated human subject. An albino rat, however, whose back has been shaved, shows no obvious cutaneous or systemic reaction after an initial exposure of three hours at this distance. In these experiments it also appeared that thyroparathyroidectomized rats showed definitely deleterious effects after irradiations of from 3 to 30 minutes. In three instances, rats which had been in a condition of latent tetany had violent convulsions, terminating fatally, within an hour after the irradiation, and in other instances less severe attacks occurred within an hour after irradiation. It was possible that this might be due to the excitement of being transferred to fresh cages, carried downstairs to a strange room, and

stimulated by the odor of ozone and the bright visible radiations from the lamps.

In the final experiments, therefore, both controls and test animals were set under the lamps, the controls being shielded from the ultraviolet light by means of glass plates. In the first experiment 26 thyroparathyroidectomized rats were divided into two groups in such a way that the weights of the controls showed the same distribution as those of the test rats; the average weight for each of the two groups was 124 grams. Irradiations were begun on the day of the operation, and the observations, discontinued on the ninth day, showed positive results. The controls, which had been shielded from the ultraviolet wave lengths, had suffered more severely from tetany, had a higher mortality, and had lost six times as much in average body weight. A second experiment was then done with 13 rats. The irradiations were begun three days before operation. The results were again positive. When the observations were discontinued 48 hours after operation, the mortality was nil for both groups, but the tetany had been less severe in the rats receiving ultraviolet light and they had lost only  $2/3$  as much in body weight as had the controls.

The conclusion is that ultraviolet light in daily doses about 50 times that used in the unhabituated human subject is beneficial to thyroparathyroidectomized white rats. It is difficult to say how much significance may be attached to this benefit. On the one hand, it is possible that the irradiation might have some favorable effect upon the body without a specific relationship to those phases of metabolism with which the parathyroids are specifically concerned. On the other hand, supposing a specific relationship to exist between the parathyroids and the irradiated skin, one could hardly expect very striking results from a slowly-acting therapeutic agent like ultraviolet light in a condition which progresses as rapidly as does the parathyroprival syndrome in the rat, so that the effects reported here and by others would seem to be significant. The experiments of Reed and Tweedy (2), who found no alterations in the blood calcium level when the blood was directly irradiated in anesthetized dogs; of Mayerson, Gunther, and Laurens (3), who did not find any rise in blood calcium during the first 8 days of

irradiation; of Swingle and Rhingold (1), who found that the positive results of their irradiation experiments were not accounted for by any appropriate changes in the blood calcium; and of Denis and Corley (4), who found no increase of calcium in either tissues or blood after irradiation with or without simultaneous administration of excess calcium—all seem opposed to the supposition that calcium is primarily concerned in this effect. It is generally agreed that the disturbance of calcium metabolism in rickets is not primary. Similarly there are many objections, which have been summarized by Dragstedt (5), to the assumption that a disturbance of calcium metabolism is the only fundamental factor in the genesis of parathyroprival tetany. These considerations suggest that the parathyroids have some function which is only secondarily related to calcium metabolism and which is in some way related to the photochemical function of the skin.

#### SUMMARY

Ultraviolet light in sufficiently large doses is beneficial to thyroparathyroidectomized white rats. Unless the experiment is carefully controlled, this favorable effect is overshadowed by the unfavorable effect of handling and bright lights upon rats in latent tetany.

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# ON THE STORAGE OF SULPHUR IN THE ADRENAL GLANDS

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Recent work, both abroad and in our own laboratory, has pointed to some relationship between the adrenal glands and sulphur metabolism. Data gathered from the literature seemed to indicate that the content of sulphur found in the adrenals is higher than in the other organs. To quote briefly some of these references, we mention Schultz (1) who found 0.964 per cent sulphur in the liver, 0.7797 per cent in the spleen, and 0.8608 per cent in the muscle tissue. Other figures (2) show that the sulphur content in the liver varies from 0.75 to 1.1028 per cent in man, while in the ox it might be as high as 1.86 per cent. In the liver from 0.9643 to 2.5 per cent in man, and 1.75 per cent in the ox. In the spleen (3) the figures seem to vary from 0.7797 per cent in man to from 1.72 to 2.23 per cent in the ox.

Work done by Katz (4) seems to give more uniform figures for the various species inasmuch as the percentage of sulphur content of muscle tissue is as follows: In man, 0.75; pig, 0.85; ox, 0.77; rabbit, 0.85; dog, 0.96; cat, 0.87; hen, 0.92; pike, 1.05.

As to the adrenal, we can refer to Aufrecht and Diesing (5) who found 3.67 per cent sulphur in the adrenals, without mentioning whether they examined human adrenals or those from an animal. Other authors do not agree with this high figure (6) (Loeper 1-1.1), but the consensus of opinion seems to be that there is considerably more sulphur in the adrenal gland of the same animal than in its other organs (7). Furthermore, it seems that this excess of sulphur is stored up particularly in the cortex of the adrenal gland. Loeper (8), who has recently made extensive investigations of the function of the adrenal in sulphur metabolism, also claims that the blood of the suprarenal vein contains from one-eighth to one-third less sulphur than the arterial blood. As the amount of sulphur in the blood after removal of the adrenals increased from 0.22 to 0.894 per cent.



Loeper (9) claimed that the adrenal fixed the sulphur in its tissue and probably also in distant tissues.

Recent work done in our laboratory by Foldes (10) on the influence of sulphur on carbohydrate metabolism has shown that repeated sulphur inunction increased the size of the adrenal gland in the rabbit, while simultaneously its sulphur content also increased. In order to establish whether in case of sulphur administration the sulphur content of various organs increases or whether we are dealing with a specific function of the adrenal gland, the following experiments have been carried out.

White rats were given daily inunctions of sulphur ointment for a period of a month. The ointment was rubbed into the skin for 15 to 20 minutes on an area comprising about one-third of the back. In these animals the sulphur content of liver, spleen, kidney, muscle tissue and adrenal glands was examined, and the results were compared with those obtained in a number of healthy rats of our stock which did not receive any treatment whatever.

The procedure to determine the sulphur content was as follows: The organs were dehydrated in absolute alcohol, then minced and dried in the desiccator over calcium chloride for 12 hours, with the help of a vacuum pump. The dried substances were weighed and each dissolved separately in hot nitric acid. To this solution, according to the weight of the substance, from 5 to 10 cc. of Benedict's solution was added. The mixture was evaporated in a porcelain dish on an electric stove. The dishes, with the remaining dry and black residue, were heated over a Bunsen burner from 10 to 15 minutes. After cooling, a 4 per cent hydrochloric acid solution was added and heated until a completely clear solution was obtained. Ten cc. of a 10 per cent solution of barium chloride were added and left to stand for a few hours, then filtered through a very fine meshed, retentive filter paper. This filter paper was put into a small porcelain crucible, dried in an oven, and heated over a Bunsen burner until complete combustion. The Benedict's solution was examined for any possible sulphur content, but hardly any traces were found.

In five normal rats the following percentages of sulphur were found:

*Liver:* 0.82, 0.71, 0.71, 0.68, 0.76. The average being 0.736.

*Spleen:* 0.712, 1.06, 0.77, 0.89, 0.85. The average being 0.856.

*Kidney:* 0.868, 0.820, 0.832, 0.801, 0.842. The average being 0.832.

*Muscle:* 0.682, 0.72, 0.73, 0.728, 0.74. The average being 0.72.

The determination of the sulphur content of the adrenal glands was made on 28 normal animals. Taking into consideration the small size of the adrenal gland in the rat we used in our first determination 10 pairs of adrenal glands and obtained a percentage of 1.6 of sulphur. With another set of 10 animals, we got the percentage of 1.55. The next experiment was done on the glands of 4 animals yielding a percentage of 1.48. With two pairs, a percentage of 1.51 was obtained, and 2 determinations, each done on a single pair of adrenal glands, yielded the figures of 1.49 and 1.47.

According to these findings the average sulphur content of the adrenal glands in the rat can be put at 1.52. While these data do not agree with the figure given by Aufrecht and Diesing, they are nearer to those mentioned by Loeper, although somewhat in excess of the latter.

In the sulphur treated animals the following percentages of sulphur were found in the different organs:

*Liver:* 0.916, 0.85, 0.823, 0.75, 1.01, 0.913, 0.82, 0.843, 0.914, 0.892. These figures vary from 1.01 to 0.75, with the average 0.893.

*Spleen:* 1.06, 1.4, 1.327, 1.1, 1.09, 0.996, 1.19, 1.02, 1.12, 1.101. These figures vary from 1.4 to 0.996, the average being 1.14.

*Kidney:* 1.04, 0.85, 0.874, 0.76, 1.18, 1.03, 0.932, 0.912, 0.946, 0.887. These figures vary from 1.18 to 0.85, the average being 0.941.

*Muscle:* 1.101, 0.98, 0.962, 0.7, 1.14, 0.842, 0.78, 0.823, 0.865,

0.812. These figures vary from 1.14 to 0.78, the average being 0.8914.

The adrenals were examined in the following order: Those of the first 2 animals were each examined separately. The figures obtained were 3.35 and 3.8 per cent respectively. The next 6 animals were examined in two groups each of 3. The percentage found was 3.90 and 3.16. The remaining two pairs of adrenals examined together gave a percentage of 3.42. Thus the figures obtained for the adrenal vary from 3.16 to 3.90, with an average of 3.526.

In comparing the figures obtained in our experiments it appears that the amount of sulphur in the liver, spleen, kidneys and the muscle tissue does not increase at all, or at least not considerably. On the other hand, the increase of sulphur in the adrenals is a striking one, ranging from 100 to 150 per cent. It seems, therefore, that the adrenal gland is the only organ examined so far capable of storing sulphur which has been introduced into the body. The sulphur in question is obviously not a part of the protein molecule. However, we are not able to tell in what form such sulphur is deposited. These findings, together with those of Loeper, seem to establish a hitherto unknown function of the adrenal gland, which is probably connected to its cortical portion. This "thiopexique" function of the adrenal cortex may have some bearing on carbohydrate metabolism, according to the experiments carried out in our laboratory by Foldes (11).

#### SUMMARY

The sulphur content of various organs of the normal rat, and of rats which had received repeated injections of sulphur, was examined.

Small amounts of sulphur were retained in the organs of the latter animals.

The physiological sulphur content of the adrenal gland is higher than that of the other organs, and after sulphur administration its increase is considerable.

In conclusion, I wish to express my sincere thanks to the

head of the laboratory, Professor M. Goldzieher, for his kind advice and assistance.

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# Abstract Department

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## Addison's disease and diabetes mellitus occurring simultaneously.

Arnett, J. H., Arch. Int. Med. 39: 698-704. 1927.

A rare and possibly unique case is reported, believed to represent the simultaneous existence of two mutually antagonistic conditions, Addison's disease and diabetes mellitus. The diagnosis of diabetes was based upon the presence of hyperglycemia, glycosuria, ketonuria, and at times a diminished plasma  $\text{CO}_2$  with symptoms of impending coma. The diagnosis of Addison's disease was based upon excessive pigmentation of the skin (a microphotograph of which is shown), arterial hypotension, asthenia, vomiting, absence of one suprarenal gland and widespread changes in the other. Homochromatosis with diabetes (bronzed diabetes) was ruled out by the absence of iron-reacting pigment and the absence of extensive fibrosis of the abdominal organs, so characteristic of this disease. The outstanding therapeutic difficulties presented by this case were hypersensitivity to insulin (presumably due to the Addison's disease) and a tendency toward the rapid development of ketosis (probably dependent upon the presence of diabetes mellitus). Judged by this case, destructive radiation of the suprarenal glands, as is practiced in some of the German clinics as a treatment for diabetes mellitus, is not a justifiable procedure.—Author's Abst.

**Blood sugar, adrenaline and sympathetic nervous system. A test for the excitability of the sympathetic.** Delbaere, L. J., Nederl. Maandschr. v. Geneesk. 14: 379-420. 1927. Abst., Chem. Absts. 21: 3681.

The hyperglucemic effect of adrenaline is used as a test for the excitability of the sympathetic. After a theoretical discussion the results of tests are given: the hypodermic or intramuscular injection of 0.001 cc./kgm. 0.1% adrenaline immediately after a meal rich in carbohydrates increased the blood sugar of normal children by at least 0.1% within one-half hour after the injection. The response was less pronounced in convalescents from severe infections, especially those with high fever, and in children suffering from acute nutritional disturbances (decompensation Herter's infantilism), exudative diathesis, or acute rickets with or without tetany. Although it seems established that the vagus has no part

in the production of hyperglucemia, a few experiments in this direction were made. The slightly antagonistic effect of histamine is attributed to an inhibition of the sympathetic rather than to a stimulation of the vagus. Atropine had a slightly synergistic effect.

**Researches on the sympathetic suprarenal lesions in some symptomatic depressive syndromes.** De Leo, S., *Neurologica* 5: 284. 1926. Abst., *Arch. Neurol. & Psychiat.* 18: 622-623. -

The author describes two cases of depression, one of which occurred in the course of a senile psychosis and the other in the course of general paralysis. In both cases he examined the sympathetic celiac ganglia and the suprarenals. In the ganglion cells in the first case he found lesions of acute type leading to disintegration of the cell body. Lesions of the dendrites and of the axons were also found. In the suprarenals the most striking feature was degeneration of the medullary cells, a small infarct, and vacuolization of the cortical elements. In the second case, the lesions of many cells in the sympathetic ganglia were more of the atrophic type, while some cells showed fatty degeneration. Lesions of the dendrites and of the axons were also marked. In the suprarenal there was hyperemia of the zonia reticulata, besides a few small focal hemorrhages. The chromaffin cells were swollen, with homogeneous cytoplasm and degenerated and poorly stained nuclei. The lesions may, according to the author, have influenced the onset of the depressive features in the two types of psychoses. The lesion of the sympathetic ganglia particularly may influence the development of hypochondriac delusions, especially in patients with defective judgment, while the lesions of the suprarenals may facilitate the accumulation of toxic substances which act on the cerebral cortex. The depressive conditions at times accompanying Addison's disease suggest a suprarenal origin for the depressive syndrome.

**Hyperadreninemia in fever (Ueber Hyperadrenalinämie bei Fieberzuständen).** von Euler, U., *Arch. f. d. ges. Physiol.* 217: 699-716. 1927.

Evidence is adduced that tissue oxidation is increased by increased adrenin action in fever.—A. T. C.

**Action of the adrenal cortex on growth (Azione della corteccia surrenale sull' accrescimento).** Fieschi, A., *Tipografia Cooperativa* 1-15: 1927.

Experiments on rabbits showed that feeding with adrenal cortex caused a greater development of the muscles and bones in experimental than in the control animals. The relative growth of

the trunk skeleton was greater than that of the limbs. The author believes this to be a hormone action of the adrenal cortex.—G. V.

**Studies on vigor. IX. Ergographic studies on adrenalectomized animals.** Gans, H. M. and H. H. Miley, *Am. J. Physiol.* **82**: 1-6. 1927.

A comparative ergographic study of the fatigability of the gastrocnemius muscles of 22 adrenalectomized and 18 normal rats was made. The absolute strength per gram muscle of the experimentals was slightly higher than that of the controls. The total work performed by the adrenalectomized animals before complete fatigue was only 1/16 of that of their controls.—Authors' Abst.

**The diagnosis of adrenal tumors with classification of adrenal tumor syndromes, and report of cases.** Gibson, T. E., *J. Urol.* **18**: 33-59. 1927.

This is a review with bibliography and a discussion of nine cases of adrenal tumor, four of which were primary. There are three types of clinical pictures from such tumors. (1) The genito-suprarenal type shows changes toward the adult male type of body, particularly of the genitalia. This is associated with a cortical tumor, either carcinomatous or benign. These may occur at any age. The medullary tumors, or neurocytoma, produce the other two types. (2) The Hutchison's type shows a metastasis to the orbit on the same side. (3) The Pepper type shows a rapid enlargement of the abdomen due to metastases to the liver. These latter types are confined almost entirely to infants.—J. C. D.

**A substance which prolongs the life of adrenalectomized cats.** Hartman, F. A., C. G. MacArthur and W. E. Hartman, *Proc. Soc. Exper. Biol. & Med.* **25**: 69-70. 1927.

Nineteen adrenalectomized cats were kept alive for periods ranging from 7 to 60 days by the injection of small amounts of an extract of adrenal cortex. Untreated adrenalectomized animals ordinarily survived only 5 to 6 days. Ox adrenal cortex was extracted with water or 0.8% NaCl. The extract was then cleared of protein and cellular debris by isoelectric precipitation. The substance which the authors name "Cortin" was then obtained by precipitation with NaCl. Epinephrine was removed by washing.

—M. O. L.

**Variations of glycogen in heart and brain, and of lactic acid and hexose phosphate in muscles in adrenalectomized rats (Variations du glycogène cardiaque et cérébral, de l'acide lactique et du lactacidogène musculaire chez les rats décapsulés).** Houssay, B.

A. and P. Mazzocco, *Compt. rend. Soc. de biol.* **97**: 1252-1253. 1927.

Fifty-seven decapsulated male white rats and thirty controls were examined six to forty days after operation. In the heart the amount of glycogen was the same in operated and control animals. The cerebral glycogen and the lactic acid in the muscles were somewhat increased in the decapsulated rats. In a number of rats the lumbar cord was cut. When the muscles of a paw were tetanized for one minute, more lactic acid and less hexose phosphate were found in the muscles of the decapsulated animals than in those of the controls. The conditions approximated those of the controls after four minutes rest.—J. C. D.

Output from adrenal anastomosed to the blood vessels of the neck (*Décharges d'adrénaline d'une surrénale anastomosée aux vaisseaux du cou*). Houssay, B. A. and E. A. Molinelli, *Compt. rend. Soc. de biol.* **97**: 1311-1312. 1927.

The adrenals of one dog were given a blood supply from the carotid and jugular vessels of a second dog. The output of adrenalin was measured by the changes in blood pressure in the second dog. Stimulation of the great splanchnic nerve and injection of nicotine into the blood stream of the donor caused marked output of adrenin.—J. C. D.

The effects of epinephrin on the partition of food stuffs in obese and normal individuals. Krantz, C. I. and J. H. Means, *J. Clin. Investigation*, **4**: 225-233. 1927.

The data obtained from a study of the respiratory metabolism in seven obese and four normal subjects were analyzed from the standpoint of the effect of injection of 0.625 mgm. of epinephrin on the partition of protein, fat and carbohydrate. In a separate series of cases studied, no significant increase in the protein metabolism was noted after the injection of such small amounts of epinephrin. The protein metabolism was considered to be at a constant level of 15 per cent and after deduction for this the respiratory quotients were interpreted in terms of fat and carbohydrate metabolized. It was found that obese individuals had more fat and less glycogen available for metabolism than did normal individuals. When a metabolic stimulant such as epinephrin was given, the most readily available food stuff was oxidized, and in the case of obese individuals, that was fat.—Authors' Abst.

Noteworthy facts on the actions of adrenalin and carcium on the heart. Murase, H. and K. Nakajima, *Journal of Aichi Medical Society*, **33**: (6). 1926. Abst., *Japan Medical World*, **7**: 146.



The authors concluded that up to a certain amount, both adrenalin and carcium accelerated the heart actions of the cold-blooded animals. Both drugs would still further accelerate the heart by the administration of second doses, but if the second dose be too large it either interrupts the heart action or paralyzes it. If carcium was given to the adrenalin paralyzed animals, the accelerating action of the adrenalin became still more marked. It was the same when adrenalin was administered in the carcium paralyzed cases.—R. G. H.

**The antagonism between quinine or quinidine and epinephrin.**

Nelson, E. E., *J. Pharmacol. & Exper. Therap.* 31: 209. 1927.

The rise in blood pressure produced by epinephrin or by splanchnic stimulation is diminished after administration of the alkaloids. Rabbit uterus and the retractor penis of the dog are inhibited by epinephrin after these drugs. The author interprets these results as indicating that quinine and quinidine exercise a specific depressant effect on the motor division of the sympathetic nervous system.—C. I. R.

**The action of epinephrin upon the cardiac rhythms.** Otto, H. L.,

*J. Lab. & Clin. M.* 13: 70-75. 1927.

Since epinephrin by virtue of the powerful accelerator stimulation it induces can cause the appearance of cardiac arrhythmia, in many instances of a dangerous or unpleasant nature, it is distinctly advisable to administer it with caution, particularly to cardiac patients or those individuals presenting a history of having had one of the cardiac arrhythmias.—Author's Abst.

**Blood pressure following adrenalectomy.** Rogoff, J. M. and R.

Dominguez, *Am. J. Physiol.* 83: 84-91. 1927.

Blood pressure measurements were made before, during and following adrenalectomy, in dogs, by Van Leersum's (carotid loop) method, which permits observations to be made on non-anaesthetized animals. Nearly all the observations included systolic and diastolic measurements. Observations, made daily, on one dog surviving double adrenalectomy about 12 days and another about 37 days, showed no significant change in blood pressure during the period of good health of the animals. A decided and progressive fall of pressure occurred a few days before death, with the onset of the terminal symptoms. The dog that survived nearly 37 days had the second adrenal removed toward the end of the period of rut.—R. G. H.

**The influence of adrenin on the vagus pulse (Der Einfluss des Adrenalins auf den Vagus puls).** Sawitsch, W. W. and E. N. Speranskaja-Stepanowa, Arch. f. d. ges. Physiol. **217**: 413-418. 1927.

Adrenin produces a stronger slowing of the heart-beat the higher the tonus of the heart-center of the vagus nerve, thereby improving the work-capacity of the center. With lowered tone the adrenin action may fail.—A. T. C.

**The effects of epinephrin on the auricular tonus waves of the turtle heart.** Sollman, T. and T. N. Rossides, J. Pharmacol. & Exper. Therap. **32**: 19. 1927.

Epinephrin abolishes tonus waves and relaxes the tonus of the auricles in three species of turtles. The loss of tonus does not occur if the waves are already absent. With very dilute solutions tonus waves are incompletely suppressed, in which case the rate is decreased, while their amplitude may be increased.—C. I. R.

**On the "Calorigenic Action" of epinephrin.** Soskin, S., Am. J. Physiol. **83**: 162-170. 1927.

Experiments are reported on 4 normal, 7 eviscerated, 2 hepatectomized and 2 depancreatized dogs. Adrenalin was administered subcutaneously in doses of 0.1 mgm. per kgm. body weight. It was found that epinephrin causes a marked rise in the oxygen consumption and a significant increase in the R. Q. of normal dogs. In eviscerated or hepatectomized dogs, epinephrin does not prevent the usual decline of the oxygen intake, or show any significant influence on the R. Q. In depancreatized dogs, epinephrin causes a definite rise in the oxygen intake, but no significant change in the R. Q. It is concluded that the carbohydrate plethora, caused by epinephrin in the normal dog, is not the essential cause of the increased metabolism which follows its administration. Insulin bears no direct relationship to the calorigenic action of epinephrin. The calorigenic action of epinephrin does not depend on direct stimulation of tissue cells, the presence of the liver being necessary for such an effect.—R. G. H.

**A note on the effect of guanidine hydrochloride upon the epinephrin output from the suprarenal gland and the sugar content of blood on dogs.** Sugawara, T. and H. Tada, Tohoku J. Exper. Med. **9**: 295-311. 1927.

Guanidine hydrochloride was given intravenously in a dose of 0.15 to 0.3 grams per kgm. of body weight to six dogs, from which the suprarenal vein blood and the ear vein blood (for the blood sugar determination) were collected without fastening, narcotizing or evoking pain. This was made possible by previously cutting the

afferent spinal nerve roots of the operative field. The drug was proved by the results of intestinal segment assays to have accelerated the epinephrin output from the suprarenal gland; five to ten times of the initial discharge was reached. The acceleration began immediately after application of the drug and lasted for several hours at least. After intravenous injection the blood sugar content increased at first. This hyperglycaemia continued half to one and a half hours, then turned to hypoglycaemia, which progressed rapidly.—R. G. H.

**Functions of the adrenal cortex and the mechanism of biological oxidations.** Szent-Györgyi, A. V., *Magy. orv. Arch.* 28: 138-143. 1927. *Abst., Chem. Absts.* 21: 2485.

In certain cases of biological oxidations, a hydrogen activation as well as an oxygen activation is required. In the plant the oxygen-activating system has the character of a phenoloxidase, that is, of an enzyme which with the aid of molecular oxygen oxidizes the labile hydrogen of phenol. Also there is present in plant tissues a corresponding aromatic substance which is oxidized by the phenoloxidase to a quinone. This quinone is reduced again by the dehydration system and thus acts catalytically as a hydrogen carrier. In certain plants there is a second aromatic substance acting as a catalyst in the oxidation system. This substance has strong reducing properties. An analogous substance in relatively high concentration was found in the adrenal cortex and appears to form a specific constituent of the interrenal system.

**Structural changes in the suprarenal gland of the mouse during pregnancy.** Tamura, Y., *Brit. J. Exper. Biol.* 4: 81-92. 1926.

Observations made on unilaterally ovariectomized mice during pregnancy showed change in the histological structure of the adrenal. Both adrenals were found to undergo modifications in structure identical with those that occur in the normal pregnant female. There was no correlation seen in the mouse between body weight, body length and the size of the suprarenal gland. The size of this gland did not always indicate its functional activity. During pregnancy the suprarenal became reduced in area. It was noted that hypertrophy of the zona glomerulosa occurs during pregnancy and at the 17 mm. stage it reaches the maximal secretory activity. Hypertrophy of the zona fasciculata may be caused by either an enlargement of cells or an increase in their number. The zona reticularis degenerates rapidly at an early period of pregnancy and at the middle of pregnancy the site of this zone is occupied by vacuoles. The hypertrophy of the medulla occurs at the closing period of pregnancy.—R. C. Moehlig.

Adrenals and solar plexus in anaphylaxis (*Le capsule surrenali ed il plesso solare nell' anafilassi*). Velardi, F., *Folia med.* 12: 452-463. 1926.

By means of vital stains a study was made of the modifications occurring in the adrenals and the solar plexus in rabbits during anaphylaxis. The modifications were of the same order in the two organs.—P. M. N.

Addison's disease, suprarenalopathies, sclerosis of the glands of internal secretion. Wakefield, E. G. and E. E. Smith, *Am. J. M. Sc.* 174: 343-357. 1927.

A clinical report of three cases of Addison's disease with a review of the literature. In case I, asthenia, nausea and vomiting with marked bronzing of the skin were the most marked symptoms. At autopsy caseous lesions were found in the suprarenals. With case II there was a series of symptoms simulating Addison's disease but the patient recovered. The authors think that this case was an instance of a toxic or inflammatory suprarenalopathy and not true Addison's disease. The third case was in a person having a familial and congenital pigmentation of the skin, alopecia totalis, and ended not unlike Addison's disease. At autopsy one adrenal was absent and there was a sclerosis of the remaining adrenal. From their own results and from the case reports of others, the authors conclude that the prognosis and treatment are equally discouraging.

—E. L.

Simultaneous determination of the blood sugar content and the epinephrin output from the suprarenal gland in the non-anaesthetized, non-fastened dog during peptone poisoning. Watanabé, M., *Tohoku J. Exper. Med.* 9: 412-453. 1927.

In the dogs, whose dorsal roots corresponding to the operation field were previously sectioned, the epinephrin liberation from the suprarenal body and the blood sugar content of the ear vein blood were simultaneously determined after an intravenous introduction of peptone in a dose of 0.1 to 0.3 gram per kgm. of body weight. Neither fastening nor anaesthesia was resorted to. The epinephrin liberation began to accelerate with a latency, of half a minute or less, reached its acme in a few minutes, and recovered in a half to two hours or later. The acceleration was from five to thirty times the initial rate in the dogs poisoned moderately or intensively. When too large a quantity of peptone was introduced, collapse developed early and death ensued within a short time; the acceleration was very slight. In general, fluctuation of rate of epinephrin discharge from the suprarenal capsule ran strikingly parallel with the symptoms of shock by peptone. The blood sugar content also fluctuated after peptone. The acme was found one quarter to

one hour after peptone, at about the midst of the depressant stage, and the level decreased then gradually to 0.08-0.05%. The lowest value was found usually two to three hours after injection, and in a further one to two hours the hypoglycaemia disappeared entirely. The moment at which the blood sugar level reached its smallest value was found therefore somewhat later than the recovery of the clinical symptoms as well as of the epinephrin discharge to their normal states. As regards blood sugar fluctuations after peptone, the de-afferented dogs did not differ from normal.

No definite acceleration in the epinephrin liberation on administration of peptone was established by the cava pocket method in experiments under anaesthesia.—R. G. H.

**Studies on diabetes insipidus. II. The diuretic substance, preliminary observations.** Bourquin, Helen, *Am. J. Physiol.* 83: 125-133. 1927.

A substance having diuretic properties has been extracted from sections of the brains of dogs, which were cut in such a way as to include only the mammillary bodies as nearly as that is possible. This substance is present in much larger quantities in the mammillary region of the brains of dogs suffering from experimental diabetes insipidus than in the same region of the brains of normal dogs, and has not been found in extracts of other regions of the brain. It is not precipitated by phosphotungstic acid. A substance having diuretic properties has also been demonstrated in the blood of dogs suffering from experimental diabetes insipidus but not in the blood of normal dogs, which is less active after the preparation has been charred, which is destroyed by prolonged boiling in a weakly alkaline solution, which is relatively stable in neutral solutions and in the dry form, and which is not precipitated by phosphotungstic acid. The substance in the mammillary region and in the blood both cause the same type of diuresis, both cause an excessive response to diuretics injected during the period in which they are acting, and both produce manifestations of thirst. Efforts to detect a similar diuretic substance in the urine have been unsuccessful.—Author's Abst.

**Sedimentation velocity of red corpuscles and the effect of various gland extracts (La velocità di sedimentazione dei corpuscoli rossi e suo comportamento in seguito all' azione di estratti ormonici).** Corsonello, P., *Giorn. di Clin. Med.* 8: 133-141. 1927.

The sedimentation velocity of red corpuscles was studied in the rabbit, according to Gardère's and Lainé's method, before and after treatment of the animals with hypophysis, adrenal, spleen, thyroid and testis extracts. All of the extracts accelerated the total 24-hour sedimentation velocity more than the partial 1- or 2-hour.

—P. M. N.

**Notes on the mental development of children exhibiting the somatic signs of puberty praecox.** Doe-Kulmann, L. and C. P. Stone, J. Abnorm. Psychol. **22**: 291-324. 1927.

From the data of 62 cases of puberty praecox containing remarks on mental development the following appear to be legitimate deductions: The rate of mental development tends to be normal or subnormal; it is seldom, if ever, really accelerated. Specific trends of mental development are probably not closely correlated with specific types of pathological development or functioning of the endocrine glands underlying the disorder. Such physical traits as height, weight, muscular development, strength, ossification of bones, closure of epiphyseal junctures, and dentition may greatly surpass the norms for children of similar ages, and quite frequently they surpass the extreme ranges for American school children of their respective ages. Precocious development of the external genitals and the secondary sexual characters is usually found, although exceptions to the rule have been described. The extent of precocious development in various elements of the sexual organs of the secondary sex characters is variable from individual to individual. Puberty praecox is considered an acquired disorder arising on a basis of pathological development or pathological functioning of the glands of internal secretion. There is no evidence pointing to a distinctly hereditary basis. A bibliography of 44 citations is appended.—Author's Abst.

**Functional relation between endocrine glands and fracture of bones** (Rapporti funzionali tra ghiandole endocrine e frattura ossea). Enriquez, P. and L. Robuschi, Arch. di fisiol. **24**: 382-447. 1926.

Following fractures of bones the thymus was found to increase in size; many thymocytes became unicellular Hassal corpuscles, and then pluricellular ones. The old pluricellular ones (true reservoirs of secretion) rapidly completed their secretory cycle. When the fracture was almost healed the thymus decreased to even less than its previous size. Injection either of fractured bones or of calcium salts may induce similar reaction from the thymus. The reaction of thymus to fracture was more accentuated in adult animals than in the very young ones. The anterior portion of hypophysis similarly reacted to fracture of bones, assuming again a foetal character. Injection of calcium salts gave the same peculiar coloration obtained after fracture.—G. V.

**Some results of endocrine therapy in behavior disorders of children:**  
A preliminary report. Geiger, Sara, Tr. Chicago Neurological Society, Abst., Arch. Neurol. and Psychiat. **18**: 1050. April 21, 1927.

Twenty children showing evidences of glandular imbalance,

who were referred to the Institute for Juvenile Research on account of behavior disturbances involving poor judgment, restlessness, lack of concentration and difficulties arising from mental deficiency or a feeling of inferiority were treated with gland extracts. These children have been studied, usually at weekly intervals, over periods ranging from six to thirty months, to determine the effect of the treatment on mentality, physique and behavior. Pituitary substance given by mouth produced no change either in the physical condition or in behavior. An attempt was not made to elevate a low metabolic rate above a high normal plus rating; with the dose of thyroid sufficient to do this, loss of body weight did not occur; however, the emotional reactions became more stable. Pituitary extract given hypodermically in increasing doses produced no change in physique; however, the children with mental defect became less restless and were not so definitely alien in a normal social group. A carefully selected diet, low in carbohydrates and fats, alone or in any combination with the aforementioned substances, produced a diminution in weight, which occurred more promptly in combination with thyroid substance. Pituitary extract administered hypodermically and thyroid substance administered orally, singly or combined, produced definite changes in behavior consisting of less sullenness, less restlessness, more stable emotions, and better concentration, leading to improved adjustments in home, school and play. The results secured indicate that there are advantages in endocrine therapy. Further data, including laboratory observations, roentgenographic study of bone growth, visual fields, growth curves, statistical data and the relation of sex problems to endocrine pathology are in course of preparation.

Some experimental and clinical facts concerning follicular hormone (Quelques faits expérimentaux et cliniques concernant l'hormone folliculaire). Brouha, L. and H. Simonnet, *Presse méd.* 103: 1619. 1926.

The earlier experimental work on the follicular hormone is reviewed. The author concludes that the term "folliculine" used by Courrier is the one of choice. The method of preparation of the hormone is briefly outlined. The clinical observations reported are five cases of amenorrhea, one case of dysmenorrhea, and one of hypoplasia of the uterus and dysmenorrhea, and two of menopause. The return of menstruation following a varying period of amenorrhea was credited by the author to the influence of the hormone. He concludes that in a certain number of cases of ovarian hypofunction and in disturbances of the menopause, the use of folliculine has given satisfactory results. It is a question whether this is due to direct action on the genital tract or to some influence on the ovary. Certain peculiarities in the responses, such as the ad-

vance of the date of menstruation or the appearance of menstruation following a single injection suggests that folliculine plays an active rôle in the process of menstruation. The clinical use partially confirms the experimental results attributed to the hormone. Observations are in progress as to whether this will substitute for the ovaries in cases of castration at operation.—J. P. Pratt.

**The relation between menstruation and ovulation in the monkey.** Corner, G. W., J. Am. M. Ass. 80: 1838-1840. 1927.

From data secured at autopsy and by exploratory operation in young mature females of the monkey, *Pithecus* (*Macacus*) *rhesus*, it was seen that menstruation frequently occurs without detectable evidence of ovulation, and is therefore apparently not dependent on the presence of a corpus luteum. However, when ovulation occurs, it seems to take place at a definite time, about twelve or fourteen days before the onset of menstruation. Menstruation without ovulation is not preceded by the so-called premenstrual changes of the endometrium, which occur only after formation of the corpus luteum. The cause and meaning of menstruation, in this species, are not at present known. Physicians in a position to obtain human material are urged to gather and study it in the light of these new facts discovered in a related species.—R. G. H.

**Ovarian hormone in water soluble form.** Dickens, F., E. C. Dodds and D. J. T. Brinkworth, *Lancet*, 212: (i) 1015-1016. 1927.

A method of obtaining oestrus-producing hormone in water soluble form from placenta is outlined. The essential steps consist of treatment with hot 7% hydrochloric acid, adjustment of the pH to 3, passage through a Sharple centrifuge, and successive treatment with saturated picric acid, acid alcohol and acetone. This method yields 1,000 rat units per kgm. of placenta, the rat unit being 0.5 mgm. of the product.—E. A.

**Observations on the activity and working power of the uterine muscle of the non-pregnant sow.** King, Jessie L., *Am. J. Physiol.* 81: 725-737. 1927.

Observations on the isolated muscle of the pig's uterus in 70 animals indicate that the circular and longitudinal layers function differently and that both pass through significant changes in activity and in working power (53 specimens) during the oestrous cycle. The work accomplished is greatest during oestrous and least at the time when the corpora lutea are at the height of development.

—R. G. H.

**Studies on vigor. XI. Relation of hysterectomy to voluntary activity in the white rat.** Durrant, E. P., *Am. J. Physiol.* 82: 14-18. 1927.



In an experiment with 26 hysterectomized and 6 control white rats observations were made by means of vaginal smears and by recording voluntary activity. The results indicate that the uterus exerts no hormonal effect on the cyclic activity of the ovary. Our observations, carried out by the revolving cage, confirm the results of the work of Long and Evans by the vaginal smear method.

Author's Abst.

**True hermaphroditism in man.** Kwartin, B. and J. A. Hyams, J. Urol. 18: 363-383. 1927.

A negro, 24 years old, showed externally hypospadias, a mass in the right inguinal canal, but no right testis. Internally there was a small uterus opening into the urethra. The left gonad was in the position of an ovary, but was an ovotestis, as sections showed. This is the eleventh case of true human hermaphroditism reported. There is a brief discussion and a list of 55 references.—J. C. D.

**A note on the preparation and properties of a female sexual hormone (menformon) in water-soluble form.** Laqueur, E., P. C. Hart and S. E. de Jongh, Lancet 212: 1126. 1927.

A resume of the authors' methods of preparation of a water soluble product of a high degree of purification.—E. A.

**The feminizing influence of the female sex hormone (menformon) on the undeveloped mammary gland.** Laqueur, E., S. E. de Jongh and M. Tausk. Deutsche med. Wchnschr. 53: 867. 1927.

Injections of "menformon" over long periods (3 weeks to 4 and 5 months) stimulated growth of the secretory parts of the mammae in immature rats of both sexes and also in mature male rats. This mammary growth influence is considered specific for the "female sex hormone."—E. A.

**On a peculiar type of intersexuality in the guinea-pig.** Lipschütz, A., Brit. J. Exper. Biol. 4: 227-244. 1927.

An abnormality of the external genital organs in 16 otherwise normal female guinea-pigs is described. Fifteen of these animals were from Estonia, one from Riga in Latvia. There were an hypertrophied penis-like clitoris and horny styles similar to those in the intromittent sac of the normal male penis. The length of the hypertrophied clitoris and of the horny styles varied much. The greatest length of the external part of the clitoris was 4 mm.; the greatest length of the horny styles was 3½ mm. The abnormalities were often asymmetrical, the clitoris and the horny styles on one side being more developed than on the other. They may even be absent on one side. The abnormal conditions of the external genital organs in these animals are identical with those described for the

castrated female guinea-pig, experimentally masculinized by testicular transplantation. It is suggested that the malformation is a peculiar type "of partial somatic intersexuality," according to the classification as given formerly by the author. This suggestion is based on the consideration that whereas the external genital organs resembled those in the male guinea-pig, there was no indication of the ovaries being abnormal or producing simultaneously female and male sexual hormones. The ovaries of the abnormal females when grafted into castrated males produced the typical female hormonal effect on the mammary glands as normal ovaries do; the engrafted ovaries of the abnormal females had no influence on the penis or on the horny styles of castrated males. The clitoris and the horny styles of the intersexual females were not affected by removal of the ovaries, whereas in the male removal of the testes causes a pronounced regression of the horny styles even in fully grown animals; the horny styles when cut regenerated; they did even after removal of the ovaries; on the contrary, there is never a regeneration in the castrated male, but only in the normal male.

—Author's Abst.

**Ovarian secretion and tumor incidence.** Murray, W. S., *Science*, 66: 600-601. 1927.

Non-breeding reduces tumor incidence in mice and delays the time of tumor appearance (207 mice used). Two hundred and ten female mice, castrated at 28-35 days, behaved much the same as non-breeding females. Two hundred and forty-one males castrated at 28-35 days did not develop tumor, thus resembling non-castrated males. Spontaneous tumors, never obtained in thousands of normal males of the stock used, may develop in castrated males which have received subcutaneous transplants of ovarian tissue (210 operated—four tumors).—Author's Abst.

**On the occurrence of the oestrus cycle after x-ray sterilization.**

**Part IV. Irridation of the adult during pregnancy and lactation; and general summary.** Parkes, A. S., *Proc. Roy. Soc. B.* 102: 51-62. 1927.

A paper containing five tables regarding the effect of x-rays on lactation, oestrus cycles and pregnancies. A summary of the author's previous work is also included in this paper. From his results the author drew the following conclusions: Irradiation during early pregnancy causes reabsorption or abortion of the foetus. During lactation the follicular disintegration produced does not affect the persistent corpora lutea of lactation. When the young females were irradiated the ova degenerated, but on the attainment of sexual maturity the normal cyclic changes were found in the accessory organs. The only exceptions were found in the animals in which the ovaries had undergone luteal degeneration. This destruction of

the Graafian follicle shows that the oestrus cycle is not dependent on the alternate maturation of the follicle and corpus luteum.—E. L.

The experimental bases for the theory of sex differentials. (*La notion des "Seuils différentiels" sa base expérimentale; son importance en endocrinologie sexuelle.*) Pezard, A., *Rev. franç. d'Endocrinol.* 4: 233-253. 1927.

The author reaffirms his previously reported idea of sex thresholds, and produces the four following "laws," based upon experimental data secured by a study of the relation of the testes to the comb of the cock, to support his case: Law of definite equilibrium is based upon the observation that four grams of testicular tissue form a neutral zone. Law of the rate of development indicates the development rate is independent of the mass if above four grams. Law of the rate of regression holds that the regression curve is the same in total castration and partial castration if the remaining mass is less than four grams. The law of angular discontinuity is based upon the observation that if, either through regeneration or graft, the testicular mass of a previously castrated animal reaches a value of more than four grams, regression ceases and growth begins. The angle in both cases coincides provided the testicular mass exceeds four grams. From these observations it is concluded that four grams is the threshold value for the comb, and that the action is an "all or none" reaction. To determine whether the other sex characters, such as sex instinct and crowing, had different thresholds, various degrees of incomplete castration were produced. The result made it possible to determine four well differentiated groups. Three of the sets of factors were produced by 4-6 grams of testicular tissue, the fourth only on an excess above this. The author believes that the substance for each action is the same qualitatively and the varying action is produced by different quantities. A number of difficult questions, such as gynandromorphism in chickens, are explained on the above hypothesis.—Bert Cunningham.

Monkey testicle grafted in man. Retterer, E., *J. d'urol. méd. et chir.* 24: 97-115. 1927. *Abst., J. Am. M. Ass.* 89. 1909.

A lawyer, aged 66 years, found that his memory was getting poor and that he became fatigued after two hours' work. He had been impotent for two years. Three months after implantation of a monkey testicle (*Cynocephalus sphinx*), his intellect, especially his memory, was greatly improved, as well as his endurance. His genital functions returned, but after twenty-eight months were decreased by one-half. Although the intellect maintained its improvement, he requested a new graft. Retterer examined the old graft and concluded that the element producing the stimulating principles is the epithelium of the seminiferous tubules; general well-being

lasts from three to four years; that is, until sufficient time has elapsed for the transformation of the epithelial covering into connective tissue.

**Studies on the physiology of reproduction in birds. XXII. Blood fat and phosphorus in the sexes and their variations in the reproductive cycle.** Riddle, O. and Frances H. Burns, *Am. J. Physiol.* **81**: 711-723. 1927.

During the ovulation cycle of female ring-doves the amount of alcohol-ether-soluble substance in the whole blood is increased to 35% above the normal or "resting" value. The phosphorus contained in this extract is increased to approximately 50% above the normal value. This well-marked cyclic increase in the fat and lipid phosphorus of the blood recurs with each ovulation period. In female doves forced to continuous egg-production the metabolism of fat and phosphorus is therefore repeatedly brought to and temporarily maintained at an unusual level. The literature on changes in blood fat and phosphorus in the reproductive cycle in animals and man is reviewed. Cyclic changes earlier observed in these doves—suprarenal hypertrophy, increased blood sugar, increased blood calcium—all reached a maximum coincident with the "ovulation period." The blood fat and phosphorus, however, attain their maximum 67 to 45 hours earlier—in the pre-ovulation stage of the cycle. Because of the known relations of the ovary to fat metabolism this earlier maximum of fat suggests that the ovary itself—rather than suprarenals or parathyroids—is more directly responsible for the entire series of changes hitherto observed in the reproductive cycle. Considered as groups, normal male ring-doves have less blood fat (1.77 g. per 100 cc.) than normal females (2.02 g.) in the "resting stage" or in any other stage of the reproductive cycle. An increased storage of fat earlier found by Riddle to characterize the female-producing ova of pigeons is thus paralleled by a higher concentration of fat in the blood of adult females. The literature dealing with blood fat as a sex-differential is reviewed. From the protozoa to man there is meagre but uncontradictory evidence that the metabolism of fat is not equal in male and female. This inequality is probably not to be regarded as a secondary sex character, but as a direct expression of the metabolic difference which one of us has earlier identified with primary sex difference.—Author's Summary.

**Ovarian follicular hormone in blood of pregnant women.** Smith, M. G., *Johns Hopkins Hosp. Bull.* **41**: 62. 1927.

A substance identical in its biological reactions to ovarian and placental hormone is present in the blood of pregnant women. Its concentration increases from the second month to the termination of pregnancy, being highest just before and during labor. There is a rapid disappearance from the blood following delivery. It can

be demonstrated in the urine just before and following labor. The amount in the placenta per gram weight is approximately twice that in the blood per cubic centimeter. The concentration in maternal blood during labor and in blood from the umbilical cord is the same.—E. A.

**Ovarian hormone.** Truffi, G., *Arch. di Scienze Biol.* 10: 147. 1927. Abst., *J. Am. M. Ass.* 89: 2148.

In his experiments Truffi used the follicular fluid of mares. A single subcutaneous injection (from 3 to 4 cc.) brought about the development of pre-oestral phenomena and oestrus in female guinea-pigs, rabbits and dogs—immature as well as sexually mature. Such phenomena regress when treatment stops. If treatment is extended to twenty or forty days, the oestral phenomena are also prolonged. In sexually mature animals, even if castrated, typical phenomena develop, such as normally appear only in the presence of corpus luteum. In immature animals, maturity is hastened and secondary sex characteristics are influenced. Liquor folliculi may thus replace both corpus luteum and interstitial gland. The ovarian epithelial element may exercise its specific hormone action without reaching the lipid element stage. In male animals follicular fluid exerts an evident antitesticular and antimasculine effect. In the guinea-pig it stops spermatogenesis and promotes the growth of the mammary gland, and in the cock it influences the growth of the comb. In order to cause such changes, it must contain the specific ovarian hormone. This hormone has a physiologic and sexual but not a species specificity.

**Protracted oestrus induced by ovarian extracts.** Taisk, R., *J. Physiol.* 63: 180-186. 1927.

Extracts of follicular fluid were injected into normal and castrated mice for periods varying from 8 to 16 days. Oestrus cornification of the vaginal epithelium continued for 7 days in castrated and 13 days in normal animals. The conclusion drawn is that continuous oestrus results when a threshold concentration of hormone is maintained.—E. A.

**The relationship between insulin and the ovaries and its therapeutic value in the treatment of uterine hemorrhage** (*Über Beziehungen zwischen Insulin und Ovarium und ihre therapeutische Verwertung bei der Behandlung von Uterusblutungen*). Vogt, E., *Zentralb. f. Gynäk.* 51: 719-735. 1927.

Vogt discusses the function and action of insulin. He also discusses at length its relationship to the general endocrine system, to the vegetative nervous system, and to the ovaries. He has used insulin with apparent benefit in the treatment of various forms of pathological uterine hemorrhage. Insulin influences the internal

secretion of the ovary and thereby affects the entire endocrine system. It also affects the duration and amount of menstruation, by reducing the hyperglycemia of menstruation. The action of insulin upon the ovaries shows the inter-relationship between the hormones, the vegetative nervous system, and the ionic content of the blood.

—J. P. Pratt.

**The effect of ovarian traumatization on the spontaneous activity and genital tract of the albino rat, correlated with a histological study of the ovaries.** Wang, G. H. and A. F. Guttmacher, *Am. J. Physiol.* 82: 335-349. 1927.

Experiments were performed on the white rat to ascertain the changes in the activity and the vaginal smears after experimental ovarian traumatization, and the correlation of these changes with the histological structure of the traumatized ovaries. Out of 28 animals, 8 showed no change in either the activity, the vaginal smears, or the cellular structure of the ovary; 4 showed castrate effects in both the activity and the vaginal smears and complete degeneration of the ovaries; 15 (53%) showed changes in both the activity and the vaginal smears; and one showed smear changes with a castrate level of activity. The change in activity was expressed in the disappearance of the normal four-day oestrous rhythm, despite the maintenance of the pre-operative daily running averages. In the vaginal smears, the normal four-day cyclic variations in cellular contents also disappeared, and only cornified epithelial cells were consistently observed. The uterus showed great hypertrophy. These changes in the activity and the vaginal smears lasted until either the traumatized ovary was removed or the animal killed. We have observed them from 40 to 170 days after the traumatization operation was performed. After the injured ovary had been removed, the usual castration effects on both the activity and the accessory sexual organs were obtained. It is the secretion from the follicular cysts which is responsible for the changes in both the activity and the accessory sexual organs found in rats whose ovaries have been moderately traumatized, since these cysts were the only structures consistently found in the injured ovaries of these animals. The only cellular element constantly present in the follicular cysts was the granulosa layer. Thus, the granulosa cells may have given out the hormone which produced increased activity, cornification in the vaginal epithelium, and hypertrophy of the uterine wall. In one animal consistent cornification of the vaginal epithelium and uterine hypertrophy were found with low arrhythmic activity, and its ovary contained neither follicular cysts nor large Graafian follicles, but only corpora lutea.—Authors' Abst.

**The hormone of the heart-beat (Ueber ein Hormon der Herzbe-  
wegung).** Haberlandt, L., *Arch. f. d. ges. Physiol.* 216: 778-788;  
789-795. 1927.

Further evidence is presented of a specific hormone controlling the heart-beat.—A. T. C.

Raynaud's disease and the pituitary (Raynaudsche Krankheit und Hypophyse). Bloch, E., *Klin. Wchnschr.* 6: 457-459. 1927.

Bloch reports a case of a woman, aged 59, with scanty menstruation every 4 weeks and of one day duration. The menopause occurred at 53 years. There was swelling of the face and hands as well as fatigue and loss of memory. A diagnosis of myxedema was made in 1919 and she was then treated with thyroid. There was a rapid improvement in her condition. She received thyroid for 5 years and was then given ovarian tablets. In 1924 the beginning of Raynaud's symptoms were confined entirely to the fingers. There was marked anemia of the fingers during cold weather; thickening of end phalanges with severe pain and asphyxia. In 1925 these attacks were uninfluenced by the weather. There were at that time marked trophic changes as well as excessive thirst and crumbling of the teeth. The patient was treated with hypophysis tablets, after which disappearance of thirst and teeth symptoms was noted. There was no change in Raynaud's symptoms. The author believes that every case of Raynaud's disease should receive pituitary injections, as other therapy is quite hopeless. Without detracting from the theoretical basis of the therapy, his evidence for pituitary involvement in this particular case is not very strong; basing it as he does on the fact that the patient had thirst and teeth involvement which were benefited by pituitary tablets by mouth.

—R. C. Moehlig.

Dosage and action of pituitary extract and of ergot alkaloids on uterus in labor. Action of epinephrine. Bourne, A. and G. H. Burn, *J. Obst. & Gynec. Brit. Emp.* 34: 249. 1927.

Bourne and Burn have studied the changes taking place in the human uterus after the administration of pituitary extract and the separate ergot alkaloids, trying to find whether the minimum dose was without danger at any stage of labor. They introduced into the uterus a rubber bag which was connected by rubber tubing to a mercury manometer. The variations in the level of the mercury were recorded by a float bearing a celluloid flag, on the end of which was an ink writing point. After the bag had been introduced and the record started, they watched the succession of uterine contractions during a period from 45 to 50 minutes. During the first 15 to 20 minutes there was usually an increase in contraction, due in part to the stimulating effect of the bag, and in part to the passing away of the inhibitory effect of the anaesthetic, as the last traces were exhaled. The tracings of contractions remained approximately regular in size during the next 30 to 40 minutes before the pituitary extract was injected. In thirteen cases studied with pitui-

trin extract it was found that two units seemed to have a valuable effect, not so much in providing a powerful stimulus to strong expulsive uterine contractions, but in regularizing such contractions and perhaps in producing co-ordination between fundal contraction and the cervical inhibition or relaxation. They came to the conclusion that a small dose of pituitary extract may be expected to produce an effect which should be useful in hastening the course of a sluggish labor, provided that it is not administered before the os is about one-half dilated. A dose of two units may be given with safety at any stage, provided there is no mechanical obstruction. They studied the action of the separate ergot alkaloids in the same way as pituitrin was studied. They found that tyramine has no value in obstetrics. Histamine in a dose of 2.0 mgms., when injected under the skin, produces a powerful but short lived effect. It appeared to exhaust the uterine activity. The specific alkaloid of ergot (ergotamine or ergotoxin) exerts a very powerful action and appeared to be an ideal agent for use after delivery. The fluid extract of ergot (British Pharmacopae) does not contain the specific alkaloid, and in view of the results they obtained it can have no therapeutic effect. They also determined that adrenalin injected into the vein inhibits uterine contraction before delivery. The administration of ether has a similar effect.—J. P. Pratt.

**Studies in acromegaly. VI. The disturbances of carbohydrate metabolism.** Davidoff, L. M. and H. Cushing, *Arch. Int. Med.* 30: 751-786. 1927.

The authors have studied a series of 100 cases of acromegaly, with special reference to carbohydrate metabolism. In this series they have found one case out of four to have glycosuria and approximately one case out of eight to have diabetes mellitus. They discuss in detail the etiology of this glycosuria. A type of adenoma, composed of chromophil cells, and accompanying acromegaly, is mentioned as the one type of tumor which is prone to cause a disturbance of sugar metabolism. The inter-relation of the pancreatic and hypophyseal secretions is also discussed, with many references to the literature. It is concluded that the pancreas and its islet tissue exerts a reciprocal effect on the hypophysis; that both pancreatic islets and hypophysis have some influence on sugar metabolism; that insulin serves to affect favorably both acromegalic and pancreatic forms of the disease; and that a hypophysectomy may offset experimentally produced diabetes. Sugar tolerance tests were also made on several patients with acromegaly, but without glycosuria. All of these were found to have a decreased tolerance for sugar. Again, in a series of six cases in which partial hypophysectomy was performed, four of the cases showed a distinct improvement in the sugar tolerance after the operation. The authors finally conclude that the glycosurias accompanying acromegaly can be ascribed



to the hyperpituitarism because: patients with acromegaly, even in the absence of glycosuria, usually have a low sugar tolerance and some hyperglycemia, whereas patients with hypopituitarism usually have a high tolerance for sugar and show hypoglycemia. The melituria of acromegaly may be recovered from spontaneously, which is seldom if ever true of pancreatic diabetes. Insulin and posterior lobe extracts have been shown to be, and insulin and anterior lobe extracts may be presumed to be, counter-active in their effects. Insulin will control acromegalic diabetes, but far less effectively than it does the more common forms of diabetes unassociated with hyperpituitarism, the assumption being that the increased pituitary activity tends to counteract its effects. The partial extirpation of the acromegalic adenoma will apparently render patients with diabetes more amenable to insulin, and may promptly lower the tendency to hyperglycemia exhibited by many of these patients even in the absence of active glycosuria.—H. M. Keith.

**Studies in the causes of dental anomalies.** Downs, W. G., *Genetics*, 12: 570-580. 1927.

Six hundred and forty-seven patients were studied. Some were taken from a hospital for the insane, others from a school for feeble-minded, and still others from private clinical cases. Two hundred and twenty-nine were normal and four hundred and eighteen showed bodily deviations more or less definitely ascribable to endocrine factors. In short, about 50% of cases of endocrine dyscrasia showed dental anomalies as contrasted with 17% in the normal subjects. Experiments were made with feeding and injecting dogs with the extracts of both the anterior and posterior lobes of the pituitary gland. Five puppies about one month old were fed extracts of anterior lobe, five were fed posterior lobe and five others were given the whole gland. Five were kept as controls. Litter mates were used in each case. When the animals were killed by litters at intervals of 4 to 8 weeks, no influence on dental conditions could be detected. Similarly negative results were obtained in 6 cases of "antuitrin" and 6 of "pituitrin" injections. A rather marked hereditary trend in dental anomalies was found in the human subjects.—R. G. H.

**Hypopituitarism: A summary of observations in twenty-seven cases followed seven years.** Eidelsberg, J., *J. Am. M. Ass.* 89: 449. 1927.

Fourteen of the 27 patients were distinctly below the average normal height for their age and sex. Fifteen were females of whom 8 had never menstruated. Of the 7 other females, 4 gave history of irregularity and scantiness, and 2 of these are practically normal at the present date. Twelve were male patients, and 6 of these

had no hair over the pubes, in the axillae or on the face. Desiccated whole gland pituitary substance was administered in doses of .1 to 5 grains daily. The greatest improvements and the greatest disappointments occurred with regard to obesity. The average loss of weight was 32 pounds. The average increase in height was  $4\frac{1}{2}$  inches. In 12 of the 27 patients, headache was an important symptom. Of the 27 patients, 11 had blood pressure varying between 86 and 100 systolic. The best results from all angles, such as growth and weight, were obtained in the younger patients, those under 20 years of age. The best results were obtained with the larger doses of the whole gland, from 50 to 75 grains (3.25 to 5 gm.) daily. Persistency and patience in the treatment were found to be very important.—R. G. H.

Is cutis verticis gyrata a symptom in an endocrine syndrome which has so far received little attention? Grönberg, A., *Acta med. Scandinav.* 77: 24-41. 1927.

A case of cutis verticis gyrata in which acromegalic symptoms were also present, is described. Nine other cases, with acromegalic symptoms, are reviewed from the literature. Although no enlargement of the sella turcica was observed in any case, the author believes that a functional disturbance in the pituitary is responsible.

—M. O. L.

The effect of pituitrin administration upon the distribution of injected fluid. Hines, H. M., C. E. Leese and H. R. Jacobs, *Am. J. Physiol.* 83: 269-274. 1927.

Pituitrin was added to Ringer's solution and administered by the continuous intravenous method to 10 unanesthetized dogs. It exerted no effect on the volume output of urine during the period of injection (usually a two-hour period). It caused a much greater blood dilution and a decreased rate of removal of the injected fluid by the tissues. Its administration was followed by a greater urine output in the three-hour post-injection period. The authors believe that this increased urine output represents primarily the elimination of the extra fluid from the blood stream, during the time of abating pituitrin action, rather than diuretic action of pituitrin per se. When injections of pituitrin and Ringer's solution were made in dogs under ether anesthesia only, a slight dilution of the blood was noted. The volume of urine excreted during the injection period was, on the average, somewhat increased. The quantity of fluid calculated to have been taken up by tissues exceeded that found in experiments on the unanesthetized animal with either Ringer's solution alone or Ringer's and pituitrin.—R. G. H.

The role of the pars intermedia in the regeneration of batracians urodeles. (Le rôle du milieu intérieur dans la régénération des

*Batraciens urodèles*). Schotté, O., *Compt. rend. Soc. de biol.* 94: (6) 1177-1179. 1926.

Schotté has reported that adult tritons and salamander larvae showed either total arrest or considerable retarding of regeneration in every case in which hypophysectomy was complete. However, the same operation has not exerted any noticeable influence on the regeneration of 45 triton larvae. Quoting several American and European authors, he says this may be understood from a reciprocal action between the thyroid and hypophysis, the thyroid substituting for the hypophysis and vice versa. Schotté agrees with Guyénot that the organism is a mosaic of regions having their own regenerative powers and losing them independently of each other. But for these regenerative powers to manifest themselves the presence of certain conditions is necessary, two of which seem to play quite a basic rôle: the sympathetic nervous system, of which he has succeeded in showing the importance, and the hormonal constitution of the *pars intermedia* regulated principally by two glands, the hypophysis and the thyroid.—R. C. Moehlig.

*Diabetic acidosis and leucocytosis*. Allan, F. N., *Am. J. M. Sc.* 174: 506-510. 1927.

Five cases of diabetic acidosis in which the symptoms simulated acute intraabdominal lesions were presented. The nausea and vomiting, as well as the leukocytosis, was misleading. The leukocytes in the absence of infection varied from 16,000-28,000. With the disappearance of the acidosis, due to treatment, the leukocytes returned to the normal level.—E. L.

*Concerning the effect of cobalt on insulin hypoglycemia in rabbits*. Blatherwick, N. R. and M. Sahyun, *Am. J. Physiol.* 81: 560-562. 1927.

Bertrand and Mâcheboeuf reported experiments on rabbits which led them to conclude that small additions of either cobalt or nickel enhanced the hypoglycemia produced by insulin. Similar experiments with cobalt have been repeated by the authors of this paper. Using standardized rabbits, no evidence for the belief that this element causes a greater hypoglycemia was obtained. The insulin was given both intravenously and subcutaneously. The favorable results of the original investigators are believed to have resulted from individual variations in the animals used.—Authors' Abst.

*Course and prognosis of diabetes mellitus in children*. Boyd, Gladys L., *Canad. M. A. J.* 17: 1167-1172. 1927.

A study of 95 patients under 15 years of age treated at the Hospital for Sick Children, Toronto, between 1918 and 1927, has led to the following conclusions: The average length of life of diabetic

children has been lengthened by insulin treatment, under which normal growth and development occur. The criterion of successful treatment consists of absence of glycosuria and maintenance of normal blood sugar for the greater part of the time. Fluctuations in tolerance are found to be frequent. Certain pathological evidence favors the belief that pancreatic regeneration may occur. The incidence of diabetic coma has not lessened, but its mortality has materially decreased, due on the one hand to insulin treatment, and on the other to earlier recognition and treatment.—A. T. C.

**Synthalin in diabetes.** Carrasco-Formiguera, R.. *Rev. méd de Barcelona*, 7: 246. 1927. *Abst., J. Am. M. Ass.* 89: 413.

The author was perhaps the first physician outside of Germany who had the opportunity to try synthalin. He confirms previous reports to the effect that the chief advantage of the new drug lies in its ability to act when administered by mouth. On the other hand, its toxicity may cause disturbances and its slow action precludes its use in emergencies. Cases refractory to insulin will probably be even more refractory to synthalin. At best, it is but a partial substitute for insulin in moderate and severe cases. In mild diabetes it can prove, however very useful.

**Insulin reactions.** Foshay, L., *Arch. Int. Med.* 40: 661-667. 1927.

The previous studies of insulin reactions have not been fruitful, because the only method of analysis has been a study of the whole blood sugar. A study of the recorded data shows that the occurrence of insulin reactions bears no direct fundamental relation to the whole blood sugar concentration. In a few diabetic patients, as in experimental diabetes in dogs, it was found that the insulin reaction is seen only when the sugar content of the blood corpuscles is low. The corpuscular glucose concentration may be accepted as an index of the glucose concentration in the cells of the fixed tissues, hence the fundamental cause of the symptoms and signs of insulin reactions is believed to be a lack of available glucose throughout the tissue cells of the body. By a determination of corpuscle sugar many impending reactions may be recognized early and completely prevented by proper prophylactic treatment. This method is especially valuable for the study of patients who are in coma, for at that time the symptoms are lacking and the physical signs may be obscured.—R. G. H.

**A synthetic substance (synthalin) with insulin action.** Frank, E., *Naturwissenschaften*, 15: 213-215. 1927. *Abst., Chem. Absts.* 21: 2320.

. Guanidine subcutaneously injected (0.3 gram per kgm. body weight) gives in a starved rabbit progressive hypoglycemia and

convulsions, 0.035 to 0.05% blood sugar after 4 hours. Subsequent feeding of glucose cannot prevent this action. The derivative agmatine (aminobutyleneguanidine) from herring sperm, synthetically prepared, 0.08 to 0.1 gram per kgm., lowers the blood sugar over 30% without visible symptoms. Larger doses give an initial hyperglucemia followed by hypoglucemia and convulsions. For aminopenuleneguanidine (one more methylene group) the intermediary stage is absent; it has an effect parallel to that of insulin. The blood sugar goes down to 0.05% and convulsions appear (0.2 gram per kgm.); a few drops of glucose solution given intravenously restore the normal condition. To increase further the hypoglucemic action lengthening of the  $\text{CH}_2$  chain is favorable, and also a second structural change (not divulged). A preparation C has been thus prepared of a convulsion dose of 0.003 gram per kgm. rabbit. This produce (synthalin is its HCl salt) acts favorably on diabetic dogs; it can be fed per os. For human consumption a dose of 20 to 25 mgm. is given per os, maximal in 4 days 125 to 150 mgm.; it makes the metabolism of 40 to 50 grams glucose per day possible. Of the synthalin, 1 mgm. is approximately equivalent to 1 insulin unit; crystalline insulin is 75 to 100 times more active than the free base of synthalin. More than 160 cases have been treated.

The effect of insulin on hypophysectomized dogs. Geiling, E. M. K., D. Campbell and Y. Ishikawa, *J. Pharmacol & Exper. Therap.* **31**: 247. 1927.

An investigation was made of the response to insulin by completely or partially hypophysectomized dogs, also of those in which escape of the posterior lobe secretion was interfered with by various means. Such animals were found to become increasingly hypersensitive to insulin, as manifested by hypoglycemia, salivation and convulsions. The anterior lobe does not seem to be involved. Extracts of the posterior lobe in large doses will protect against both hypoglycemia and convulsions, but in small doses protect only against convulsions. The authors suggest that the pituitary as well as the thyroid is involved in the production of the variable response of normal animals to insulin.—C. I. R.

Diabetes mellitus. Glassberg, B. Y., M. Somogyi and A. E. Taussig, *Arch. Int. Med.* **40**: 676-685. 1927.

A case of diabetes mellitus is reported which showed the following peculiarities: Beginning as a mild case, it rapidly became more severe and at one time showed an allergic reaction to insulin. For a period of some months the patient proved relatively refractory to insulin, responded only to enormous doses of insulin and slipped into coma or precoma as soon as these doses were reduced. During this period the patient did not respond better to fractional

doses of insulin than to an equivalent single dose: on the whole, the latter was more effective than the former. In ordinary diabetes the reverse is true. To a moderate degree, the patient's response to insulin seemed to be increased by the simultaneous injection of parathyroid extract. Later, the response to insulin increased, and the case again became an ordinary, moderately severe diabetes. It is shown that the patient's failure to respond in the usual manner to insulin can be explained neither by a destruction of insulin in the body nor by its excretion in the urine. It is suggested that in this case, as perhaps in other similar ones reported in the past few years, the diabetes was due not only to a lack of pancreatic secretion, but also to a lack of muscle enzyme (phosphates, insulin complement, glycomutin).—Authors' Abst.

**The initial hyperglucemic effect of insulin.** Guardabassi, M., *Ann. fac. med. chir.* **29**: 147-177. 1927. Abst., *Chem. Absts.* **21**: 3963.

A transient hyperglucemia is caused by subcutaneous, and more distinctly by intraperitoneal, insulin injections. It is absent or very slight in thyroidectomized animals, while thyroid feeding exacerbates both hyper- and hypo-glucemia and the toxic effect. Adrenal disease or adrenalectomy has no effect. The hyperglucemia is pronounced in diabetics and absent in castrated animals, although the latter are highly sensitive to insulin. The data are followed by a lengthy discussion on the influence of the various hormones through the medium of the liver.

**Experiments on phloridzin glucosuria. VII. Metabolism in phloridzin diabetes on an unbalanced protein diet** (*Untersuchungen über die Phlorrhizinglucosurie. VII. Das Stoffwechselgeschehen im Phlorrhizin-Diabetes bei einseitiger Ernährung mit Eiweiss*). Hanisch, Sofie and P. Junkersdorf, *Arch. f. d. ges. Physiol.* **217**: 264-278. 1927.

Provided excess of protein is fed the characteristic hypoglucemia and fatty infiltration of the liver are not produced.—A. T. C.

**Studies concerning the influence of potassium iodide and thyroid preparations upon the blood sugar curve.** Holsti, Ö., *Acta med. Scandinav.* **66**: (45) 461-466. 1927.

The author presents data of 27 blood sugar tests on 6 subjects who presented a subnormal blood sugar curve. He found that the administration of potassium iodide had no effect on the blood sugar curve, whereas thyroid medication caused a rise in all cases, persisting for at least a month after the thyroid medication had been stopped. Improvement followed the medication in 3 cases (50%) coincidentally with the rise of the blood sugar curve, or at a somewhat later period according to the author. The cases here studied

were: Myxoedema 1, bronchopneumonia 2, acute nephropathy 2, tonsillitis recidivans 1.—H. J. J.

**Bone development in diabetic children. A Roentgen study.** Morrison, L. B. and I. K. Bogan, *Am. J. M. Sc.* 174: 313-319. 1927.

The authors made a study of 68 diabetics which were under 15 years of age. They found that the bone development was in advance of the chronologic age with diabetes of recent onset, but with diabetes of long standing the bone development was below the chronologic age. Bone atrophy was observed in eight of the cases, but all of these children were less than eight and a half years old.

—E. L.

**Absorption of insulin from the alimentary tract of depancreatized dogs, when protected by blood serum.** Murlin, J. R. and Estelle E. Hawley, *Am. J. Physiol.* 83: 147-161. 1927.

Observations on 5 depancreatized dogs proved beyond a doubt that insulin protected by blood serum from the proteolytic destruction of the digestive enzymes can be absorbed in significant amounts from the alimentary tract. In some instances the respiratory quotient was raised quite as high as following subcutaneous injection. In several instances the urine was made entirely sugar-free, although the dog was on full diet containing meat. The effect on blood sugar was not so sudden or so great as when insulin is given subcutaneously. The liver seems to protect the body against the shock-like effects of a sudden access of insulin to the general circulation. Hypoglycemic shock was not seen following alimentary insulin even in huge doses. Four dogs have been kept alive, 81, 125, 41 and 91 days, respectively, after complete pancreatectomy and while on full diets. The dog which survived longest was pregnant, but lived 67 days after birth of the pups.—R. G. H.

**The action of insulin on the respiratory metabolism of the isolated mammalian heart** (*L'azione della insulina sul ricambio respiratorio del cuore isolato di mammifero*). Peserico, E., *Arch. di fisiol.* 23: 488-508. 1925.

Insulin increases the gaseous exchange and the respiratory metabolism of the normal isolated heart, and brings back to normal the low metabolism of the isolated diabetic heart. In both cases the amount of oxygen consumed and of carbon dioxide produced do not correspond to the total amount of glucose which disappears during the action of insulin. According to the author, insulin, instead of transforming the glucose into a more easily oxidizable form, is rather a direct activating element in preparing from the glucose the substances whose energy is used by the muscular fiber in the first phases of its contraction.—G. V.

**Respiratory quotient curves in diagnosis in diabetes.** Petty, O. H. and W. H. Stoner, *Am. J. M. Sc.* **171**: 842-846. 1926.

Twenty cases of normals, diabetic and renal glycosurics were studied by means of the glucose tolerance and basal metabolism tests. These authors found it necessary to make other tests besides the conventional glucose tolerance test for diagnosis. With the normals the respiratory quotient rose from the normal fasting level of 0.82-0.85 to 0.96, or 1, while with the diabetics the fasting respiratory quotients were 0.65-0.80 and rose but very little after the ingestion of the dextrose. Where renal glycosuria was present, the respiratory quotients were the same as in the normals. From their results the authors conclude that respiratory quotient studies made before and during the glucose tolerance test are a direct index of the sugar-burning ability of the individual. They also state that diabetes mellitus can be diagnosed earlier by this method than by a glucose tolerance test.—E. L.

**Variations of phosphorus content in muscular tissue during insulin hypoglycemia** (*Le variazioni del contenuto in fosforo del tessuto muscolare durante l'ipoglicemia insulinica*). Piazza, G., *Arch. di farmacol. sper.* **42**: 28-32. 1926.

Inorganic phosphorus (method of Bell and Doisy) and muscle sugar (Condorelli's method) were determined in small portions of rabbit muscle before and after injection of insulin. During insulin hypoglycemia there was neither augmentation of the organic phosphorus nor of the hydrolysable phosphorus portion.—P. M. N.

**Insulin therapy in carcinoma** (*Tentativi di terapia insulinica nel carcinomatosi*). Ponticaccia, L. and D. Campanacci, *Giorn. di Clin. Med.* **7**: 430-435. 1926.

Insulin hypoglycemia caused a slackening and an inhibition of development in experimental tumors. In six cancer cases insulin had good influence only on the weight, appetite and digestion.

—P. M. N.

**Observations on the use of synthalin in the treatment of diabetes mellitus.** Rabinowitch, I. M., *Canad. M. A. J.* **17**: 901-904, 1927.

Seven cases are reported. In the majority synthalin was effective, but in one or two non-effective, and in certain others a recurrence of glycosuria could not be cleared up by synthalin alone. It is noted that whenever a response to synthalin is obtained the resultant body-weight is less than that obtained on insulin balance, and it is suggested that the extra weight may be due to insulin oedema. Rabinowitch concludes that synthalin is effective in diabetes, but that on account of the variations found in results with it, it should only be at present employed where the metabolism of patients can be carefully observed.—A. T. C.



**Sugar tolerance as an aid to diagnosis.** Rowe, A. W., J. Am. M. Ass. **89**: 1403-1407. 1927.

An extensive series of sugar tolerance tests has been made with pure galactose. Healthy males were found to have a constant tolerance throughout life, but females, starting at a level below the male in the prepubertal years, exhibit a rising tolerance with sexual development and in maturity possess a level superior to that of the male. The menopause seemingly causes a retrogression toward the male level. Castration in the male does not produce any change; in the female, it causes a lowering which may reach the prepubertal level. Pregnancy lowers the mature tolerance, and menstruation seemingly shows a like tendency. Disturbed function of the several endocrine glands produces changes in the tolerance, the pituitary and the suprarenal exercising the greatest and the thyroid the least influence, if the testis is excluded. A variety of non-endocrine conditions, among which lesions of the central nervous system, syphilis, primary anemia, malignant tumors and liver diseases may be enumerated, tend to lower the tolerance, while serious renal disease may increase it.—R. G. H.

**Further contribution to the study of the action of insulin on the ferments** (*Ulteriore contributo all'azione dell'insulina sui fermenti*). Sammartino, U., Arch. di farmacol. sper. **42**: 17-27. 1926.

The author has experimentally demonstrated that in the reaction mixtures: diastase and starch; catalase and hydrogen peroxide; lipase and tributyrin, the addition of insulin does not modify the reaction velocities.—P. M. N.

**Blood sugar content and insulin treatment of dermatoses.** Simon, F., Arch. f. Verdauungskr. **37**: 363. 1926. Abst., J. Lab. & Clin. Med. **12**: 1121.

According to the author, a marked increase in blood-sugar value occurs in psoriasis and in furunculosis. In cases of psoriasis higher values are said to be noted in males than in females, while in furunculosis the increase is declared to vary within somewhat narrow limits. Blood-sugar value is said to exhibit an increase in the majority of cases of eczema, and to vary within wider limits. Highest values were encountered in relapses and in chronic cases, and relatively high values in eczema in diabetes mellitus. Insulin treatment of these dermatoses, which are accompanied by increase in blood sugar value, is declared to lead first to a temporary increase and later to a decrease in blood-sugar value. Thus, it is pointed out, pruritus is prevented and predisposition of the skin to injuries due to activity of bacteria is diminished. Simon is of the opinion that insulin may, through its increase in the alkalinity of the blood, exert a favorable effect upon many diseases of the skin.

**The effect of insulin injected into the cerebrospinal fluid.** Supniewski, J. V., Y. Ishikawa and E. M. K. Gelling, *J. Biol. Chem.* 74: 241-246. 1927.

In three rabbits and six dogs insulin injected into the cerebellar cisterna caused only a slight decrease of sugar and phosphates in the blood, and in some cases an increase of these substances. Insulin incubated with fresh cerebrospinal fluid does not lose its hypoglycemic properties. Probably the explanation is that owing to the large size of the insulin molecule it passes from the cerebrospinal fluid into the circulation at an exceedingly low rate.—M. O. L.

**The use of synthalin in diabetes** (*Zur synthalinbehandlung der Zuckerkranken*). Umber, F., *Deutsche med. Wehnschr.* 7: 27. 1927.

Synthalin is a derivative of guanidine, a nucleoprotein split product. The author treated 200 cases of diabetes with synthalin, which is supposed to lower the blood sugar and increase glycogen storage, but is not effective in coma. The article is illustrated with graphs. His patients responded by lowering and eliminating glycosuria, but most showed only a slight drop in blood sugar. There was never a normal glycemia in spite of a glycosuria. The best results were obtained from a combination therapy with insulin and synthalin. Non-diabetic glycosurias were as refractory to synthalin as to insulin. On synthalin therapy the weight increase was not like that with insulin; only three cases (of two hundred) gained from two to three kgm. The author also reports good results in children in combination therapy, insulin and synthalin. In surgical cases, insulin is the choice. The weak point in synthalin therapy is the toxic symptoms it produces. These appeared in 47% of the author's cases. (The average dose used was 25 mgm every other day for the adult.) The symptoms which appeared were: loss of appetite, malaise, headaches, sweating, oppressive feeling in stomach and pain, vomiting, diarrhea, and, in four vasomotor patients, tachycardia.—H. J. J.

**Calcium studies in jaundice.** *With special reference to the effect of parathyroid extract on the distribution of calcium.* Cantarow, A., S. M. Dodek and B. Gordon, *Arch. Int. Med.* 40: 129-139. 1927.

The study was undertaken to compare the response to parathyroid extract in normal and in jaundiced persons. The series consists of fourteen cases of jaundice of various types and intensity. The blood clotting time, which was within normal limits in every case, was found to be reduced by parathyroid extract as in normal individuals, from 5.65 per cent, the maximum from 6-12 hours after the injection. The serum calcium values varied from 9.3 to 12 mgm. per 100 cc., slightly beyond normal limits, the response to parathyroid extract not being as marked as in normal persons. The

variations in the calcium content of whole blood was the striking feature of the study, the values ranging between 4.8 and 12 mgm. per 100 cc., bearing no relation to the coagulation time, degree, type or duration of the jaundice. This wide variation was the most marked difference observed between normal and jaundiced blood, the normal figures being 6.43-9.61 mgm. per 100 cc. Similar variations were observed in plasma calcium. The injection of parathyroid extract was followed by a marked decrease in the degree of variation. At the end of six hours, and particularly after twelve hours, the range in jaundiced patients was practically identical with that in normal individuals. The whole blood calcium level seemed to be independent of that of serum, two patients with identical serum values showing marked variation in whole blood calcium. The favorable effect of the hormone on the tendency of injured jaundiced tissue to bleed is due to the increased coagulability of the blood and to the diminished permeability of the capillary walls.

—Authors' Abst.

**The rôle of toxins in parathyroid tetany. I. An attempt to control tetany by the oral administration of kaolin.** Larson, E. and L. A. Elkourie, *Am. J. Physiol.* 83: 231-236. 1927.

Kaolin given orally to 12 dogs did not have any decided effect in preventing or controlling tetania parathyreopriva. It was shown that kaolin does not adsorb guanidine in vitro from either an acid or alkaline medium. Guanidine was not adsorbed in significant amounts from either the ileum or the colon of an anesthetized dog during a period of one hour.—R. G. H.

**Effect of parathyroid hormone on blood coagulability. (With special reference to jaundice).** Zimmerman, L. M., *Am. J. M. Sc.* 174: 379-388. 1927.

Due to the danger of post-operative bleeding from surgery in the presence of jaundice, this author studied the effect of parathyroid hormone on blood coagulation. The coagulation time in normal and icteric patients, as well as the calcium level of the blood, was determined before and after the injection of parathyroid hormone. There was no constant effect on the coagulation time after the administration of the parathyroid hormone. From his results the author concludes that increasing the calcium content of the blood does not diminish the coagulation time either in the presence or absence of jaundice.—E. L.

**I. The effect of the parathyroid hormone on gastric secretion. II. The calcium content of gastric juice.** Austin, W. C. and S. A. Matthews, *Am. J. Physiol.* 81: 552-559. 1927.

The effect of parathyroid extract (parathormone) on the gastric response to histamine was studied in four dogs with Pavlov

pouches. It was found that if the parathyroid hormone influence is severe and prolonged, and the water balance of the body is unfavorable because of restricted intake and increased elimination of water, the gastric response of the dog to histamine may be decreased. If the parathyroid hormone is administered in large amounts, and the water balance of the body more favorably maintained, the gastric response of the dog to histamine is normal. After overdosage of the dog with parathyroid hormone, the Pavlov pouch continues to secrete until the beginning of hemorrhage, when it stops completely and suddenly. The calcium content of pure gastric juice of the normal dog is 5 to 6.5 mgm. in 100 cc. The calcium content of gastric juice of the dog is not greatly influenced by administration of the parathyroid hormone in amounts sufficient to elevate the blood calcium to the level of 18 or 19 mgm. in 100 cc.—R. G. H.

**Parathyroid in the treatment of tropical sprue.**—Baumgartner, E. A., *Am. J. Trop. Dis. [etc.]*, 7: 381-391. 1927.

Three quite severe cases of tropical sprue are described in some detail. All of these cases had low blood calcium and definite evidences of tetany and the effect of parathyroid extract on them is studied by noting the blood calcium changes. The first case entered with well marked signs of tetany, her blood calcium was 6.2 mgms. per 100 cc. blood. Following the administration of 5 cc. of Collip's parathyroid extract there was a definite rise of blood calcium to 8.1, which fell again and was not raised by a second series of injections of 4 cc. of parathyroid preceded by a blood transfusion. A third series was again effectual in causing an increased blood calcium. Thereafter the dry extract of parathyroid was used, 1/10 grain thrice daily for a month and then at intervals of a few days. The second case was given the dry extract daily over a period of four months, although she entered with a normal blood calcium and with no sign of tetany. At the end of two months the blood calcium decreased. Six weeks later signs of tetany were present. The patient left the author's charge, continued for some months, then developed definite tetany spasms and died. A third case with a very low blood calcium improved markedly on the dry extract with calcium lactate. It is believed the dry extract can help raise blood calcium, that if given over a long period it may help deplete the tissue reserve calcium.—Author's Abst.

**Parathyroid preservation.** Terry, W. I. and H. H. Searls, *J. Am. M. Ass.* 89: 966-967. 1927.

In the standard operation of partial thyroidectomy, a surprisingly large number of parathyroid glands are being removed as a result of their frequent relationship to the anterior and lateral capsule of the thyroid gland. Their removal or injury is very frequently followed by moderate transient evidence of parathyroid

deficiency. By careful inspection, these bodies may often be identified and preserved. Routine preservation of the lateral capsule is an additional safeguard which should be adopted as a simple modification of present technic. Even though the symptoms of this deficiency are transient and followed practically always by complete recovery, it will be conceded that parathyroid tissue is of extreme value to the patient and should not be removed or injured.

—Author's Abst.

**Parathyroid hormone and the calcification of fracture callus.** Lehman, E. P. and W. H. Cole, J. Am. M. Ass. 89: 587-588. 1927.

In 13 to 14 white rats, the injection of parathyroid extract did not hasten the calcification of fracture callus, as judged by breaking strength. In fact, the breaking strength of the callus of the treated rats was slightly less than that of the controls.—R. G. H.

**Tumors of the pineal gland.** Haldeman, K. O., Arch. Neurol. & Psychiat. 18: 724-754. 1927.

Two cases of glioma of the pineal gland are reported with complete clinical and pathologic characteristics. In view of the contradictory results obtained in the experimental work on pineal gland feeding of animals and of defective children and on the destruction of the pineal gland in animals, it is impossible to draw any conclusions regarding the function and significance of this gland. A tumor of the pineal gland in a child is occasionally accompanied by precocious sexual development and adiposity or general overgrowth, which with symptoms of internal hydrocephalus make up the syndrome designated by Pellizzi as "macrogenitosomia praecox." One hundred and thirteen cases of tumor of the pineal gland are summarized in chronological order. Tabulation of the microscopic picture presented in the 113 cases shows: sarcoma, 24 cases; teratoma, 22 cases; cyst, 14 cases; glioma, 11 cases; pinealoma, 10 cases; hyperplasia, 4 cases; carcinoma, 4 cases; adenoma, 4 cases, psammoma, 2 cases, and unclassified, 18 cases. The syndrome of "macrogenitosomia praecox" was observed in 16 cases of pineal tumor, all in males between the ages of 3 and 16 years. Blindness or impairment of vision occurred in 45 cases, or in more than one-third of the total. The most important of the eye signs in cases of pineal tumor are paralysis of upward movement, diplopia, abducens paralysis, nystagmus, ptosis, and absence of the pupillary light reflex. Of the 102 cases in which the sex was reported, 78 occurred in males and 24 in females. The incidence was greatest during the second decade (29 cases), although 28 patients were reported between 21 and 30 years of age, and 24 under 11 years. No conclusion can be drawn from the two cases of hypoplasia or absence of the pineal gland. A bibliography of 157 citations is appended.—Author's Abst.

**Effects of prolonged administration of desiccated spleen and red bone marrow on the blood forming centers of rabbits.** Leake, C. D., *J. Pharmacol. & Exper. Therap.* **31**: 216. 1927.

One group of rabbits were bled daily for 15 days; a second received 1 gm. desiccated spleen and bone marrow in equal weight for the same period; the third group served as controls. At the end of this period, the first group showed extensive hyperplasia of the bone marrow with a red count below 2,000,000. The second group showed moderate marrow hyperplasia and a red count above 6,000,000. The control group showed normal fatty bone marrow and a count ranging between 5,000,000 and 6,000,000.—C. I. R.

**On three cases of thymus death of infants.** Takashima, T., *Journal of Hokuetsu Medical Society*, **41**: (4 and 6). 1926. *Abst., Japan Medical World*, **7**, 147.

The author reports the pathologico-anatomical findings in three cases of thymic death—a 27-day-old boy, a 2 months old boy and a 9 months old boy. All these three died while sleeping without the least noticeable changes during sleep by their parents. At autopsy they were all found to have had hypertrophy of the thymus, especially of the cortical layer of the organ, and had specific thymic endocrine intoxication features.

**A comparison of the action of natural and synthetic thyroxin (Vergleichende Untersuchung der Wirkung von aus Schilddrüsen gewonnenem Thyroxin und von synthetisch bereitetem).** Abderhalden, E. and J. Hartmann, *Arch. f. d. ges. Physiol.* **217**: 531-534. 1927.

Natural and synthetic thyroxin produce the same action on the growth and metamorphosis of tadpoles.—A. T. C.

**The relation of thyroxin action to the sympathetic nervous system (Beziehungen der Thyroxinwirkung zum sympathischen Nervensystem).** Abderhalden, E. and E. Wertheimer, *Arch. f. d. ges. Physiol.* **216**: 697-711. 1927.

Thyroxin produces its action through the sympathetic. When action through the sympathetic is inhibited by ergotamine, thyroxin no longer produces action on metabolism.—A. T. C.

**Langhans' proliferating goiter.** Bircher E., *Beitr. z. klin. Chir.* **139**: 383. 1927. *Abst., J. Am. M. Ass.* **89**: 1288.

In the past twelve years, Bircher has seen thirty-six cases of Langhans' proliferating goiter (adenocarcinoma, according to Eiselsberg and Erdheim). He did not find it to be malignant clinically, but it has certain characteristics that separate it from the main goitre group. It has a strong predilection for childhood, and it is

refractory to iodine. Insufficiency of the pulmonary circulation, with weakening of the power of the heart from dyspnea caused by compression of the trachea, was frequent. Both hyperthyroid and hypothyroid phenomena were seen. The tendency to recur is strong and is manifested early.

**Control of hyperthyroidism by thyroidectomy.** Elliott, C. A., J. Am. M. Ass. 89: 519-522. 1927.

The status of 100 patients from six months to six years after thyroidectomy performed for the relief of hyperthyroidism, is as follows: Seventy consider themselves perfectly well; thirty are conscious of some disability; all are carrying on their usual work. Forty-one show evidence of definite visceral injury as the result of previous hyperthyroidism. Of 14 cases of exophthalmic goiter in which operations were performed within 3 months of the onset of symptoms, only one shows residual visceral damage. Four patients are considered to have persisting but not disabling hyperthyroidism insufficient to require operation. Five patients are definitely hypothyroid, and are benefited by thyroid extract. Laryngeal nerve injury occurred temporarily in 6 cases; in 2 the injury has persisted. Reoperation for thyroid remnants was necessary in 6 cases.

—Author's Abst.

**The rôle of thyroid and parathyroid glands in growth of heart and lungs.** Hammett, F. S., Am. J. Anat. 39: 219-238. 1927.

A report and interpretation has been made of the growth responses of the heart and lungs to thyroid and parathyroid deficiencies initiated at different ages during the period of active post-natal growth of the albino rat. A general growth retardation is produced. This is due to the dependency of the heart and lungs on the effectiveness of the growth of the body as a whole, the which is lowered under the experimental conditions. Hence the conclusion is that the growth of these organs is not specifically related to either thyroid or parathyroid function. The increment of gonadal incretory activity which occurs at puberty exerts its characteristic influence on the response to the glandular deficiencies.

—Author's Abst.

**The rôle of thyroid apparatus in the growth of liver, kidneys and spleen.** Hammett, F. S., Am. J. Anat. 39: 239-266. 1927.

A report and interpretation has been made of the growth response of the liver, kidneys and spleen of male and female albino rats to thyroid and parathyroid deficiencies initiated at successive stages of development during post-natal growth. There is no evidence that the growth of the liver, kidneys or spleen is specifically related to thyroid activity. The growth retardation which occurs is attributable to the relation of the type of metabolism characteristic

of the individual organ, to the retardation in effectiveness of the growth processes of the body as a whole, resulting from the lowering of the metabolic rate on the thyroid removal. The increment of gonadal incretory activity which takes place at the pubertal adjustment so acts on the metabolic substrate of the three organs that their sensitivity to the general effects of thyroid deficiency is greatly enhanced, and weight is lost instead of gained. There is no evidence that parathyroid activity has any specific relation to the growth of the liver or kidneys. The data show that the toxemia of parathyroid deficiency has a specific influence on spleen weight. It is probable that this is an expression of an influence on spleen volume exerted through the autonomic nervous system, rather than of an influence on spleen growth as such. Puberty exerts its characteristic influence in accentuating the sensitivity of these organs to parathyroid removal.—Author's Abst.

**Studies of the thyroid apparatus. L. Interpretative generalizations from the differential development observed in conditions of thyroid and parathyroid deficiency.** Hammett, F. S., *Am. J. Physiol.* **82**: 250-260. 1927.

From an analysis of a very extensive body of original data, Hammett concludes that distortion of differential development follows both thyroid and parathyroid removal. With the exception of the hypophysis, the submaxillaries, and possibly the spleen, this is not due to any specific relation of glandular functions to organ growth, but to the general metabolic disturbance induced by the deficiencies. The growth of some organs is more resistant and that of others is more sensitive than that of the body as a whole. The basis of this differential reaction lies in the relation of the metabolic processes of the organs in question to the bodily economy as a whole. The distortion is consistent in direction and produces a distinctly modified type of structural organization. The broader aspects of this finding are referred to in their relation to evolutionary development.—R. G. H.

**Studies on Metabolism. VI. Experimental hyperthyroidism.** Kunde, Margaret M., *Am. J. Physiol.* **82**: 195-215. 1927.

Extended experiments were carried out on seven dogs. It was found that no significant change occurs in the basal metabolism for 7 to 12 hours after the administration of a single dose of Kendall's thyroxin (intravenously) or desiccated thyroids (orally). Following this, an appreciable increase in the heat production occurs, which is most marked on the second day. After daily repeated doses of either desiccated thyroids or Kendall's thyroxin, the basal metabolism progressively increases, reaching a maximal three weeks or more after administering the initial dose. The maximal increase in the heat production resulting from experimental hyper-



thyroidism is 120% above normal in the dog with intact thyroid glands and 170% above normal in the previously thyroidectomized animal. This rise in metabolism is always accompanied by fever. Tachycardia and a disturbance in the conductive mechanism of the heart may both occur as a result of induced hyperthyroidism in the dog. The influence on the body weight of experimental hyperthyroidism depends entirely on an undetermined nutritional state. Some dogs display a peculiar ability to retain a constant body weight during several weeks of advanced hyperthyroidism on a previously determined maintenance diet. Others may lose 35% of their initial body weight. Diarrhoea, tenesmus and bloody stools may occur as a result of hyperthyroidism. Severe skin lesions of an eczematous character may occur in some dogs during the crisis of hyperthyroidism. Exophthalmos cannot be demonstrated in the dog, but in the rabbit the administration of thyroid substance results in a pronounced exophthalmos, provided the rabbit has previously been in a myxedematous condition, due to thyroidectomy. Hyperglycemia and glycosuria do not occur in the dog during experimental hyperthyroidism. The pathological changes in the thyroid gland during advanced hyperthyroidism consists essentially in a generalized disintegration of the gland with elongated follicular cells containing oval nuclei, and fibroblastic in appearance. Iodine injected intravenously in the form of potassium iodide does not reduce the basal metabolism of normal dogs. In the dog iodine in the form of Lugol's solution is ineffective in reducing the high basal metabolism or in preventing the metabolism from increasing during the ingestion of thyroid substances. Our results fail to support the theory that some of the clinical symptoms of either hyperthyroidism or exophthalmos are due to a perverted secretion, since all of the cardinal symptoms of a disturbance in the functional activity of the thyroid gland, excepting cretinism and myxedema, can be produced in either the dog or the rabbit under certain conditions, by the administration of thyroid substances obtained from the glands of normal animals. A quantitative relationship between the amount of thyroid substance ingested and the increase in the basal metabolism does not exist, neither is the catalytic theory of Plummer and Boothby adequate for explaining the results of the present experiments on hyperthyroidism. The degree of toxicity resulting from the ingestion of a given amount of thyroid substance varies markedly with different animals of the same species and depends on some condition of the cells, which at present seems closely related to water metabolism and dehydration phenomena. The thyroidectomized dog and rabbit are more susceptible to the ingestion of thyroid substances than animals with thyroid glands intact. In a thyro-parathyroidectomized dog, in a tetanoid state, the administration of thyroid substances exerted a marked influence on the control of parathyroid tetany.

**Experimental cretinism. I. A rachitic-like disturbance in extreme hypothyroidism.** Kunde, M. M. and A. J. Carlson, *Am. J. Physiol.* **82**: 630-638. 1927.

A study was made of 404 thyroidectomized rabbits shown by their weight curves to be actually hypothyroid. It was found that cretin rabbits (thyroidectomized between 2 and 3 weeks after birth) develop a condition of disturbance in skeletal development which fundamentally stimulates clinical rickets. This is not due to a dietary deficiency. This rickets-like condition is accompanied by severe anemia. It is characterized by a normal or slightly depressed concentration of the blood calcium and a low acid soluble phosphorus of the serum.—R. G. H.

**Experimental cretinism. II. The influence of the thyroid glands on the production and control of experimental rickets.** Kunde, M. M. and L. A. Williams, *Am. J. Physiol.* **83**: 245-249. 1927.

Experiments were made upon 46 rats. It was found that no amount of cod liver oil added to a ricket-producing diet is adequate to prevent the development of rickets in cretin rats as determined from histological studies of the epiphysis. Supplying antirachitic vitamins in the form of vitamine-rich foodstuffs to a nutritious diet consisting of table scraps failed to prevent the occurrence of rickets.

—R. G. H.

**Thyroid gland substance implantations.** Kurtzman, H. and H. Hubener, *Zentralbl. f. d. ges. Med.* **54**: 1666. 1927.

This article reviews in brief the various methods of transplanting thyroid gland. All of these methods had negative results as to the continued growth and functioning of the gland. The substance was, after a period of time, absorbed and scar tissue formed. The authors have treated three myxoedematous cretins by thyroid gland substance implantations. The thyroid gland was scraped and the substance injected subcutaneously into the cretins by means of a pressure syringe. In one case the subject, aged 11, showed improvement after the treatment with a mental awakening. The second subject, age 13, showed no improvement at all. The third child, with a mental age of two and a half years and with osseous maldevelopment, could utter only unintelligible sounds. After three injections over a period of one year the child tried to repeat spoken words, was livelier and became more active mentally. The authors conclude that the resulting effects were by no means over-estimated, but furnish proof that mental and physical improvement may be obtained by injection of thyroid tissue in myxoedematous cretins.

—L. L. Stanley.

**Adiposity of pituitary and thyro-pituitary origin in the adult: its diagnosis and treatment.** Masterman-Wood, J. L., Practitioner, 119: 165-172. 1927.

Four cases are briefly presented.—J. C. D.

**Exophthalmic goiter and diabetes (Ein Kombinationsfall von Jod-basedow und Diabetes [Zugleich ein Beitrag zu den insulin-refraktären Diabetesfällen]).** Orator, V., Deutsche Ztschr. f. Chir. 201: 402-406. 1927.

The author reports a case of a man, 47, who nine years previously was afflicted with arthritides and rheumatism, at which time he developed glycosuria, which promptly subsided on diet. In 1927 he was treated for atherosclerosis with Sajodin, and out of his symptomless enlarged goiter he developed hyperthyroidism—also symptoms of diabetes, glycosuria 1%, which insulin (20 units 2 to 3 times per day) did not wholly control. Following thyroidectomy, the glycosuria cleared up without any more insulin, and the patient was discharged as cured of both diabetes and hyperthyroidism.

—H J. J.

**Radiation therapy in malignant diseases of the thyroid gland.** Portmann, U. V., J. Am. M. Ass. 89: 1131-1135. 1927.

Of 166 patients treated or untreated, 28.3% are living more than one year, and 24, or 14.4%, more than three years since they first came under observation. Among the 125 patients who could be treated, 37.6% are living more than one year, 24, or 18.8%, more than three years, and 12.8% for five or more years after treatment was instituted. Apparently the best results are obtained by operation followed by irradiation, for in this group 22.6% of the patients are "five-year cures"; while 20, or 36.6%, are living more than three years after treatment. If this plan of treatment is followed in all cases, radiation will be applied in some cases, in which the tumors are small, localized and encapsulated, and might therefore be cured by surgery alone; nevertheless, the final results indicate the advisability of applying radiation in every case of malignant disease of the thyroid gland. The explanation for this observation may lie in the fact that apparently the cellular structures of many malignant growths of the thyroid are sensitive to radiation because of their fetal or embryonic origin, and because metastasis must take place through small blood vessels or lymphatics, which are also comparatively susceptible to radiation. In the author's experience, treatment of thyroid diseases with radium has been somewhat less satisfactory than with roentgen rays on account of a tracheitis which has occurred in almost all cases. It is deemed necessary in each case to treat the upper mediastinum as well as the gland area, and this is practically impossible with radium. In treating malig-

nant disease, it is important to prevent the occurrence of malignant disease, if possible. About 2% of all thyroid cases presented malignant disease, and since 90% of the malignant conditions of the thyroid gland originate in fetal adenomas, the author believes that all adenomas of the thyroid should be removed as a prophylactic measure. This is especially true in later life, during the years when a malignant condition most frequently develops. Prevention is more important than treatment.—R. G. H.

The iodine content of the thyroid gland of various types of cattle and its relation to the glandular condition. Von Fellenberg, T. and H. Pacher, Mitt. a. d. Geb. d. Lebensmittelunt. u. Hyg. 18: 265-289. 1927. Abst., Chem. Absts. 21: 3941.

Analysis of 80 different thyroid glands shows little relation between the iodine content and other conditions of the gland. The iodine content generally was not dependent upon the size. In certain bovine species, it varied inversely to the gland size. The absolute iodine content increased with the weight of the gland. A low iodine value accompanied a low content of colloidal matter and small follicles. Single species showed different thyroid weights and contents, so that external conditions as environment, climate, iodine, food, etc., may have more effect than actual glandular condition.

The action of iodine preparations on the metamorphosis of axolotls (Ueber die Wirkung der Jodpräparate auf die Metamorphose der Axolotl). Zawadovsky, B., A. A. Titajev, Z. M. Perelmutter and N. A. Raspopowa. Arch. f. d. ges. Physiol. 217: 198-203. 1927.

Thyroxin in single injection of 0.01 mgm. produces complete metamorphosis of Axolotls of 10 grams average weight. Tyrosine and tryptophane given with simultaneous iodine injection, and di-iodotyrosine and di-iodotryptophane in doses up to 30 mgm. do not produce this complete metamorphosis. The latter compounds cannot be compared with thyroxin, and can only serve as material for thyroxin production in the thyroids of the animals tested.

—A. T. C.

# Endocrinology

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### THE MORPHOLOGY OF PARS INTERMEDIA OF THE HUMAN HYPOPHYSIS\*

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MINNEAPOLIS

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#### INTRODUCTION

It is very evident from such reviews of the pituitary problem as the one by Geiling (1), that we are in the midst of an

\* Aided by a grant from the research fund of the Graduate School, University of Minnesota.

unusually rapid transition period with reference to the conceptions of the functions of the different parts of the hypophysis. The tendency seems to be to greatly limit the sphere of its influence.

Due to its small size and location in the interior of the organ, pars intermedia is one of the least understood parts of the gland. Judging from some of the discussions found in the medical literature, some writers lack a concrete idea of the actual magnitude of the tissue known as the intermediate portion of the human hypophysis.

The primary purpose of this note is to call attention to the great variation in the actual weight of this part of the hypophysis as determined by fairly accurate volumetric methods. The procedure consists of making serial sections of the organ and by means of a projection apparatus tracing the enlarged outline of the various portions on heavy standardized paper. These areas are cut out and weighed. If the weight of the fresh gland is known, it is easy to calculate what proportion of that weight is represented by any particular subdivision of the gland. Further details may be obtained from a previous publication (2).

#### IS THERE A TRUE PARS INTERMEDIA IN THE ADULT HUMAN HYPOPHYSIS?

Many investigators have commented in general terms on the small size and great variability of the intermediate lobe of the human hypophysis. Plaut (3), on this account, holds that it is a rudimentary organ in man, and hence of little or no functional significance in the human body. Therefore such conceptions as hypofunction, hyperfunction and dysfunction of this lobe have little or no foundation.

Kasche (4), while admitting that there are always chromophilic cells in the intermediate region and closely associated topographically with the nervous lobe, does not consider that there is sufficient morphological evidence to justify its being designated a special gland concerned with metabolism. As a result of the application of the technique of Maurer and Lewis (5) on fresh human material, he was unable to find cells with the special characteristics of pars intermedia of lower animals. Like sev-

eral other investigators, he concludes that these chromaphilic cells are essentially like the basophilic cells of the anterior lobe proper.

The view that there is no *pars intermedia* in adult man homologous to that of lower animals is also held by Erdheim (6) and Dayton (7). On account of the unusually extensive investigations into the normal and pathological structure of the human hypophysis made by Erdheim, his views should have considerable weight. Dayton examined over 100 normal adult hypophyses and some from infants, as a result of which he concludes that either the anlage of *pars intermedia* of the human embryo disappears entirely or gives origin to mucous glands or to small basophilic cells, neither of which should be regarded as *pars intermedia*. The mucous glands disappear before the adult stage is reached. Dayton further argues that all the colloid vesicles and associated cells are derived from the anterior lobe because the cells forming the walls of these cysts may be cytologically exactly like the cells of the anterior lobe proper. He claims that in pregnancy, castration and certain pathological changes of the reproductive glands, the cells forming the walls about the colloid of *pars intermedia* undergo the same changes as take place in the cells of the anterior lobe.

In short, while it is conceded that there is some sort of epithelial tissue between the cleft (remains of Rathke's pouch) and the nervous lobe, or actually invading the latter, its homology with *pars intermedia* of lower animals is in doubt. However, at the present stage it would seem—as pointed out by Lewis and Lee (8)—that it is best to retain the term "*pars intermedia*" ("*pars infundibularis*" of the juxtaneural portion of Tilney's terminology) for this tissue and the related colloid, even if it does differ somewhat from that of animals. There are also both gross and microscopic differences in structure of *pars intermedia* of different animals. If it should finally be demonstrated (which is doubtful) that in man it is developed entirely from the anterior lobe, and that the posterior wall of Rathke's really disappear, then a revision of the terminology might be desirable from a morphological point of view. From a functional standpoint, nothing can be said till more knowledge of the physiological processes carried on by this portion of the hypophysis has been established in a wide range of animals.

## HISTOLOGY OF PARS INTERMEDIA IN MAN

The histology of this region of the hypophysis has been worked on from various angles by many other investigators besides those mentioned here; but since several of the more recent publications give the essential literature, a comprehensive review will not be necessary. Erdheim's paper (6) contains a very extensive bibliography of several hundred titles. The clearest conception of the detailed relations and general histology is found in the recent paper by Lewis and Lee (8), which contains excellent illustrations of microscopical preparations and reconstructions, as well as a concise discussion of the related literature. Their study is based on serial sections of 30 human hypophyses, ranging in age from birth to 73 years, and on many other individual sections. Since our own work corroborates theirs, only a

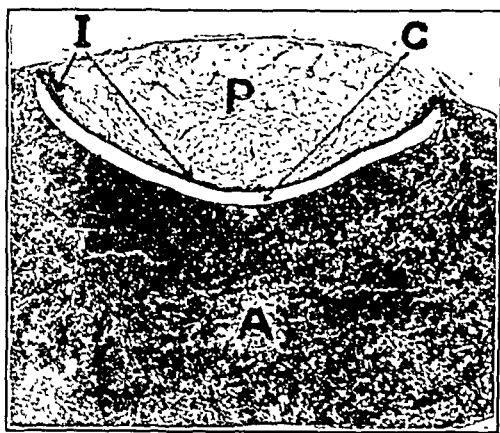


Figure 1. Photograph of a horizontal section through the middle of the hypophysis of a human newborn to show the general appearance of pars intermedia (I). A, anterior lobe; P, posterior or nervous lobe; C, cleft or residual lumen of Rathke's pouch.

very hasty sketch as deducted from the literature and from investigations that have been done in this laboratory will be given, and that merely for the purpose of giving a general background to the volumetric data to be submitted.

In the fetus, after the hypophysis has assumed its general form, there is a fairly uniform and distinct stratum of epithelial elements, several cells in thickness, between the cleft and the nervous lobe. This presents the general appearance of the pars intermedia of the usual laboratory animals, although there is



great need for further application of finer cytological technique to determine the degree of similarity that actually exists.

This condition usually persists till about birth. A general view of a newborn hypophysis is shown in figure 1. This is a horizontal section showing the general relations of pars intermedia (I), which is merely the narrow black border on the anterior surface of the nervous lobe (P), forming the posterior wall of the cleft (C). It is distinctly thicker at both lateral edges near the point where it comes in contact with the anterior lobe (A).

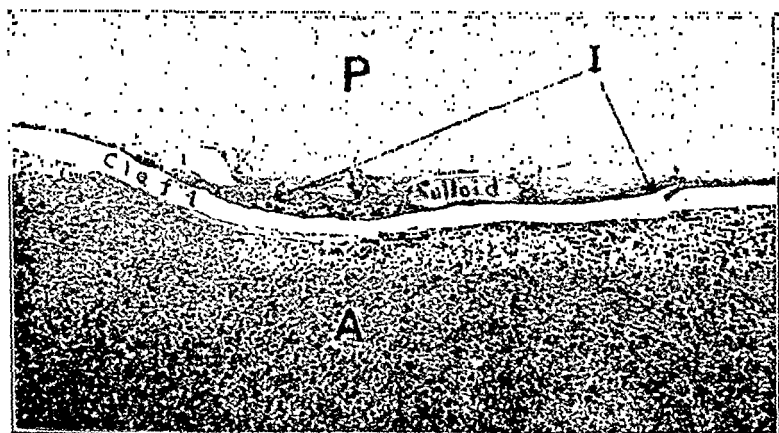


Fig. 2. Photograph of the intermediate region of a horizontal section through the middle of the hypophysis of a 6-year-old child to show the relation of the irregular epithelial masses and colloid to the more uniform stratum characteristic of the newborn and fetal hypophysis. I, pars intermedia containing several accumulations of colloid; A, anterior lobe; P, posterior lobe.

During early childhood much irregularity occurs, due to diverticula and tubular outgrowth from pars intermedia into the nervous lobe, as shown in figures 2 and 3, which are from a 6-year-old child. Figure 3 is at a sufficiently high magnification to show clearly the extension of pars intermedia and the residual lumen or cleft into the nervous lobe as branched tubules (D) with wide lumen. Figure 4 is a still higher power view to show particularly the appearance of some of these tubular outgrowths as seen in cross section (G). The reason why Dayton (7) and others have regarded these as mucous glands is evident. Notwithstanding the fact that there is a general structural resem-

blance to mucous alveoli and that Guizzetti (9) claims that the micro-chemical reactions of the substance which they secrete is that of the mucins, additional micro-chemical data are necessary to establish the mucous character of these tubules. The recon-

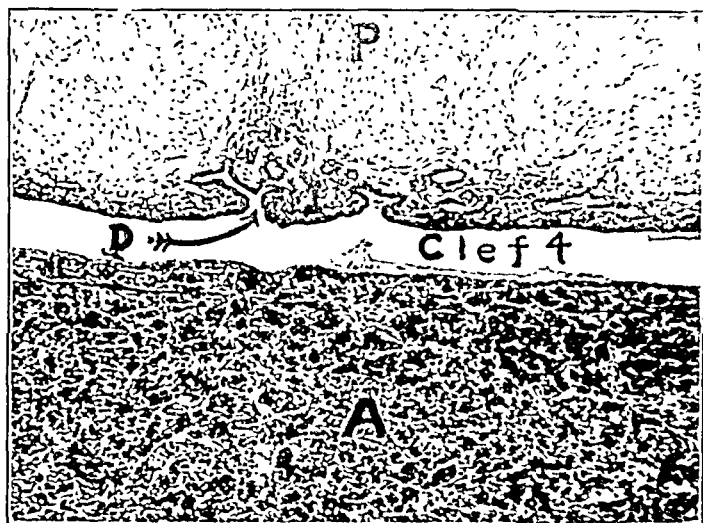


Fig. 3. Photograph of a more limited region of pars intermedia of the same hypophysis as shown in figure 2, but at a higher magnification, to show how the cells lining the posterior wall of the cleft grow into the posterior lobe (P), as tubular diverticula (D). I, pars intermedia; A, anterior lobe.

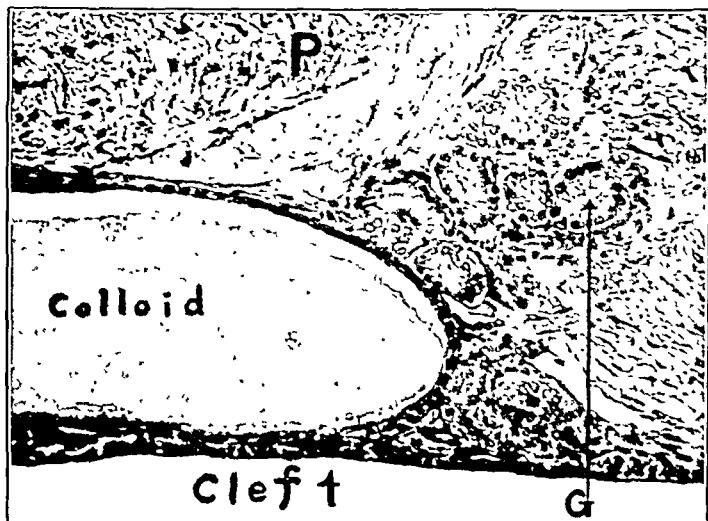


Fig. 4. Highly magnified view of a colloid vesicle or cyst and cross section of the tubular outgrowths from pars intermedia—already shown in longitudinal section and under lower power in figure 3. P, posterior lobe; G, gland-like tubules from pars intermedia in cross-section.

structions of these tubules and the detailed drawings by Lewis and Lee (8) suggest at least a glandular character.

The accumulation of a variable amount of colloid both in the cleft and in the above mentioned diverticula (see figures 2 and 4) further complicates the picture. Colloid cysts in this region may thus be derived from the accumulation of colloid in isolated portions of the cleft or in the more differentiated tubular or gland-like outgrowths. The presence of small amounts of colloid in the inner end of some of the cells lining these tubules is described by Lewis and Lee (8). This is of considerable importance in connection with the origin and significance of the colloid—a subject that is still in a very unsettled state (10). As the colloid masses get larger and larger there is a tendency for the surrounding cells to become flatter and flatter, as is seen in figure 4.

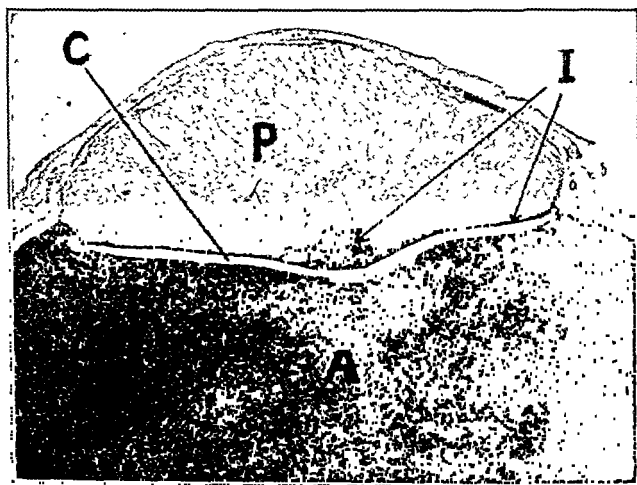


Fig. 5. Photograph of a horizontal section of the hypophysis of a 6-year-old child to show the general extent of pars intermedia (I) at the same magnification as in figure 1. A, anterior lobe; P, posterior lobe; C, cleft.

Another method of colloid formation often described, especially in the anterior lobe, but which probably also occurs in the intermediate, is by degeneration of the central cells within a group of cells. It is thus frequently impossible in the adult stage to say how much of the colloid in the region of pars intermedia should be considered a part of pars intermedia and how

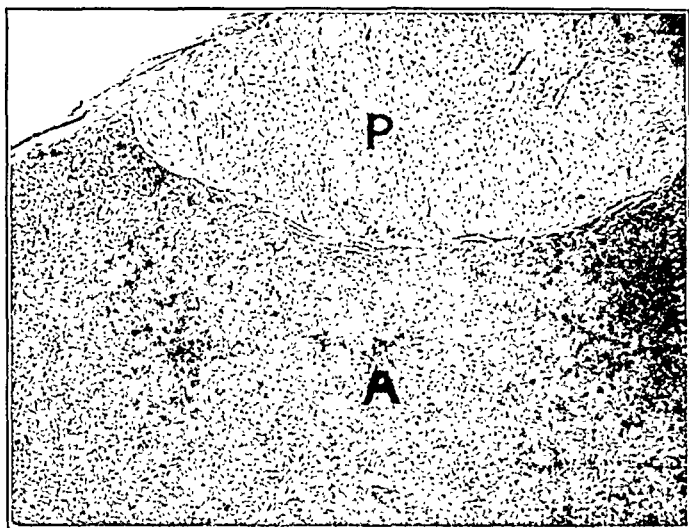


Fig. 6. Photograph of a horizontal section of a normal male adult, human hypophysis to show the extremely small size to which pars intermedia may be reduced. In this case it consists of an incomplete layer, a single cell in thickness, and hence not evident in the photography. Same magnification as figures 1 and 5. A, anterior lobe; P, posterior lobe.



Fig. 7. Photograph of a horizontal section of a normal male adult human hypophysis to show the maximum development of pars intermedia. Same magnification as figures 1, 5, and 6. A, anterior lobe; P, posterior lobe; I, pars intermedia. The cleft is distended with colloid, which was cracked during sectioning, resulting in some pieces being displaced.

much is in the cleft proper and strictly not a part of pars intermedia.

The pars intermedia of a 6-year-old child at the same magnification as in figure 1 is shown in figure 5. The dark area extending from the central portion of pars intermedia into the nervous lobe is tissue derived from pars intermedia as just described. There is still visible a thin continuous sheet of cells separating the posterior lobe from the cleft (C). For a further description the book by Cooper (11) may be referred to.

Finally, in the adult great variability is encountered. The two extreme conditions as far as size is concerned are illustrated in figures 6 and 7, which are photographs of normal adult hypophyses at the same magnification as in figures 1 and 5, so that figures 1, 5, 6 and 7 are directly comparable. In figure 6 pars intermedia is reduced to a single layer of cells, usually less than 10 microns in thickness. The lumen of the cleft is obliterated except in a few small areas. Colloid in this particular case is also found in such small masses that they are not visible at the magnification here employed. At the other extreme, as shown in figure 7, there is an abundance of epithelial cells which form a prominent layer, usually very irregular in thickness. The amount of colloid varies greatly and is independent of the amount of epithelium. In the particular case shown here the colloid is mostly in the cleft, which may thus persist in its entirety in the adult. The tubular, gland-like diverticula are no longer visible.

The cells in the adult are still roughly divisible into three types. There are the cuboidal or low columnar cells forming a more or less imperfect stratum between the anterior lobe or the cleft, as the case may be, and the nervous lobe. Then there are the cuboidal or flattened cells which form a wall about the colloid masses that are outside of the cleft proper. And, finally, there are the polygonal and round basophilic cells scattered about in the neuroglia tissue of the nervous lobe. In figure 7 the wide, dark area (I) posterior to the cleft is composed largely of this latter type. Masses of these cells may become isolated and apparently detached from the tissue bordering on the cleft. The wide variation in the compactness of this epithelial tissue is one of the sources of error in the quantitative method here employed. A variable amount of neuroglia tissue of necessity is included in

those cases where the epithelial elements are mixed with posterior lobe tissue.

There is some difference of opinion as to the origin of these basophilic cells (7), (8), (9). They have some characteristics in common with the basophilic cells of the anterior lobe. They have been taken for neoplasms, but they are so regularly present that such a view is untenable (12).

Some of the cells lining the cleft, mostly on the posterior side, have been described as possessing cilia. They are said to occur in small patches. Bryant (13) seems to regard them as sensory elements and found them present in nearly all fresh human hypophyses examined. Strange to say such ciliated cells have never been seen in any of the series examined in this laboratory, now numbering well over 200.

#### THE RELATIVE SIZE OF PARS INTERMEDIA IN ANIMALS

In order to appreciate more fully the relative amount of tissue that pars intermedia constitutes in the human hypophysis, the available literature on quantitative determinations on animals might be summarized to advantage. This will be done in the order of percentage which pars intermedia constitutes of the epithelial part (pars buccalis or glandular portion) of the hypophysis. Only adults will be considered unless there is no significant difference between the percentages in young animals and adults.

*Frog*.—Atwell and Woodworth (14) found that in 4 specimens pars intermedia varied from 12.1% to 36.4% and averaged 24.8% of the glandular portion of the hypophysis. It is upon this form that much experimental work on this lobe has been done.

*Cat*.—In 5 specimens examined also by Atwell and Woodworth (14) pars intermedia varied from 11.7% to 23.3%, with an average of 16.9%.

*Rabbit*.—From a very comprehensive analysis of all but the pars tuberalis of the hypophysis of 61 male and 62 female rabbits, Björkman (15) found that pars intermedia averaged 15.7%.

*Guinea pig*.—Pars intermedia of 8 normal animals varied from 7.6% to 16.3% and averaged 10.6%, according to Rowles (16).

*Albino rat*.—Jackson (17) found in 4 adult males a variation from 6.6% to 13.0%, the average being 10.5%. In 4 adult females the extremes were 6.1% and 8.3%, and the average 7.2%. Slightly lower figures are given by Addison and Adams (18) on a more uniform series consisting of 7 males and 7 females weighing very close

to 200 grams each. In the males the extremes were 7.0% and 12.5%, average 9.8%, and in the females 4.8% to 7.7%, average 6.0%. Since the anterior lobe is absolutely much greater in the female than in the male, the actual weight of pars intermedia is 25 per cent more in the female than in the male in spite of the lower percentage. In neither case was pars tuberalis taken into consideration.

*Urodel.*—In 18 specimens belonging to 13 different species, Atwell and Woodworth (14) found a minimum of 3.6% and a maximum of 13.7%, the average being 6.8%.

*Woodchuck.*—In 16 males and 14 females of the species *Marmota monax*, the writer (19) obtained as low as 1.9% and as high as 7.7%, with an average of about 5.0%, both sexes being combined and pars tuberalis disregarded. Although pars intermedia of the male is apparently 50 per cent larger than that of the female, the data are so recorded that the variability for each sex separately cannot now be determined.

The mean values of pars intermedia has thus been found to vary in animals from 5 per cent of the epithelial portion of the hypophysis to 25 per cent. Even within the mammalian realm the range is from 5 to 17 per cent.

#### RELATIVE SIZE OF PARS INTERMEDIA OF THE HUMAN FETUS AND NEWBORN

Atwell and Woodworth (14) analyzed 4 fetuses ranging in age from about 7 fetal months to full term and found from 1.0 to 3.4 per cent (average 2.5 per cent) of the glandular portion was pars intermedia. A more extensive study by Covell (20) on the growth of the prenatal hypophysis of 98 specimens shows that in fetuses 25-100 mm. in length, pars intermedia represents 3.5 per cent of the glandular portion. From then on there is a slight decrease in the percentage (but, of course, an absolute increase in weight) till at birth it is only 2.4 per cent, the range being from 1.5 to 3.3 per cent, which agree well with the figures given by Atwell and Woodworth. In terms of the whole hypophysis at birth, pars intermedia represents slightly less than 2 per cent.

#### ABSOLUTE AND RELATIVE WEIGHT OF PARS INTERMEDIA OF NORMAL MALE ADULT HUMAN HYPOPHYSIS

The data presented here are based on a volumetric analysis of 111 normal male hypophyses from 20 to 76 years of age. The

material was obtained through the co-operation of the Department of Pathology, University of Minnesota, during a period of six years (1921-1927). For this service we wish to express our appreciation to the various members of the Pathology staff. Only perfect glands from cases of sudden and usually accidental death, where no significant pathologic change was found at autopsy, are included. Hence, it represents as nearly normal material as is obtainable. Due to the routine method of obtaining the organ, the infundibular stalk and pars tuberalis are not included. Atwell and Woodworth (14) found that pars tuberalis of the newborn may equal pars intermedia, while Covell (Thesis, University of Minnesota, 1926) in 3 adults found it only about one-half the volume of pars intermedia. Pars tuberalis being continuous with pars intermedia, with no sharp line of demarcation between them, an arbitrary plane across the stalk at the upper level of the anterior lobe was taken as the division point. This was the only consistent method of handling the material.

The 30 normal cases involved in a preliminary report (21) are included in order to increase the reliability of the results. The method and nature of individual figures are illustrated in two previous papers (2), (21). The data have been worked up by recognized statistical methods in order to test the significance of such differences in weight as seem to exist at various ages and body lengths. The writer is indebted to Dr. C. M. Jackson and Dr. R. E. Scammon for advice on statistical methods. Only approximate body weights are available, so that no attempt has been made to determine any correlation with body weight. The general observation has been that no correlation exists in human adults between weight of the hypophysis and body weight.

All the epithelial elements posterior to the region of the cleft is included under the head of parenchyma of pars intermedia. The colloid includes that which is in the cleft as well as that which is outside of the cleft proper, but in the region of pars intermedia. There seems to be no good reason for separating the colloid that is obviously within the cleft from that which is apparently outside of the cleft but in its neighborhood. The latter is so often in a recess or diverticulum derived from the cleft, and still in communication with portions of the cleft proper, that it seems best to make no distinction, although some of the colloid in the cleft may have been derived from the anterior lobe,



a subject that is discussed more fully in a previous publication (10).

*Frequency distribution of the weight of pars intermedia*  
In figure 8 is shown the distribution of the weight of the epithelium (parenchyma). In nearly a third of the cases the weight lies between 1 and 2 mgm. In 80 of them (72 per cent of total number) it is less than 5 mgm. Only 17 of the entire 111, or 15 per cent, have more than 8 mgm., and only one has as much as 20 mgm.

Figure 9 is a similar graph showing the distribution of the colloid, the weight of which is somewhat greater, but of about

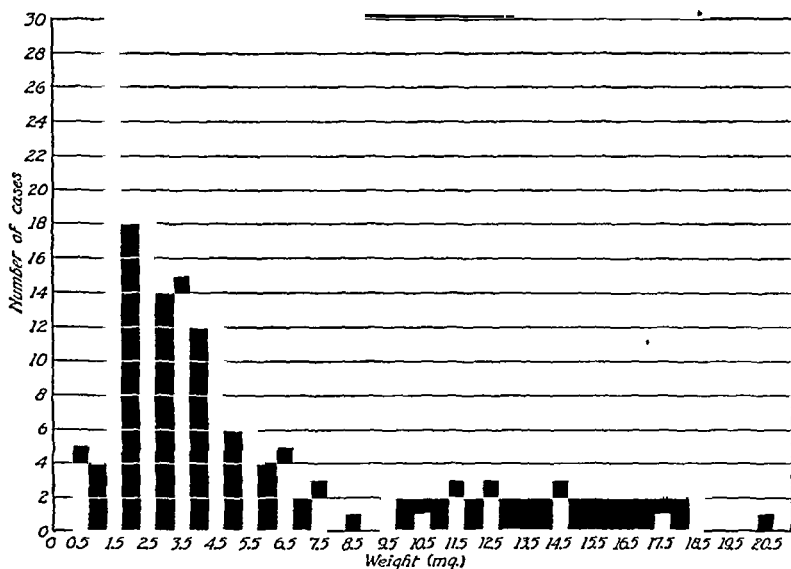


Fig. 8. Frequency graph showing the distribution of the weight of the epithelium (parenchyma) of pars intermedia of 111 normal male adult human hypophyses.

the same order, and has the same skewness towards the low values.

A frequency graph of the combined weight of the parenchyma and colloid is shown in figure 10. Even if the colloid is included as part of pars intermedia, 79 (71 per cent of total number) have less than 12 mgm. and only 9 (8 per cent) have more than 24 mgm.

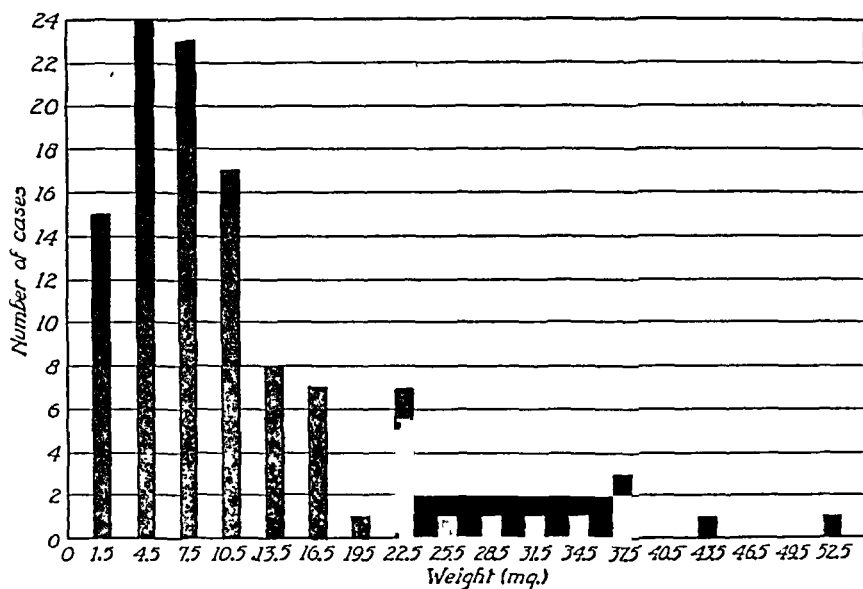


Fig. 9. Frequency graph showing the distribution of the weight of the colloid associated with pars intermedia of 111 normal male adult human hypophyses.

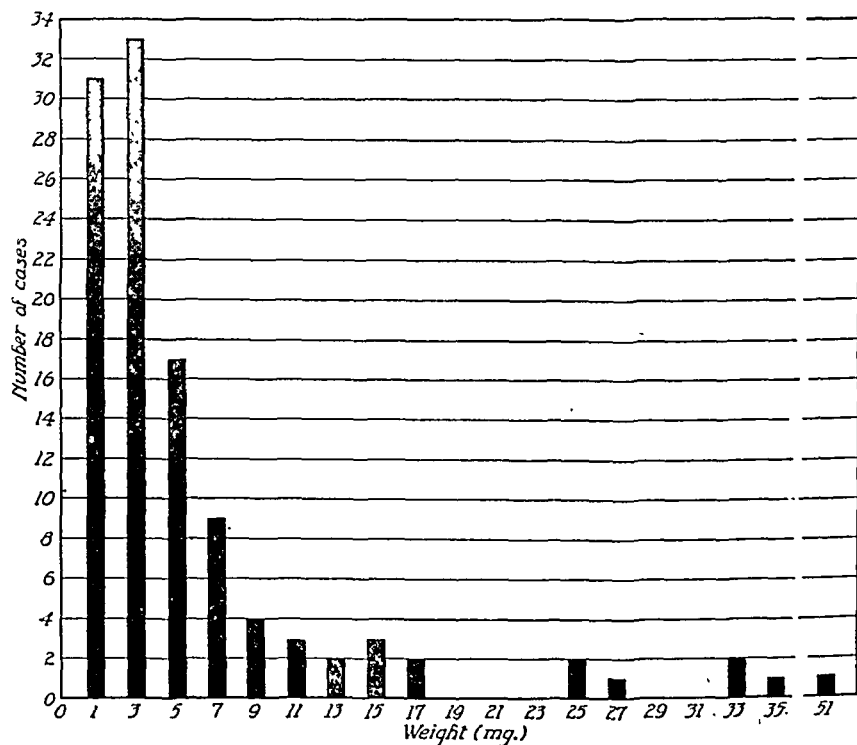


Fig. 10. Frequency graph showing the distribution of the combined weight of the epithellum and colloid of pars intermedia of 111 normal male adult human hypophyses.

*Coefficient of variation.* For purposes of comparison with other parts of the body, the coefficient of variation

$$\left( \frac{\text{Standard deviation}}{\text{mean}} \times 100 \right)$$

has been calculated for the various parts of the hypophysis. This shows that the colloid has the extremely high coefficient of variation of 137. The epithelium of pars intermedia is next with a coefficient of 94. The coefficient of the combined weight of epithelium and colloid of pars intermedia is 89. These figures are much higher than those for the other lobes and the entire hypophysis, the coefficient of variation of which are: posterior lobe, 29; anterior lobe, 21; and the entire hypophysis, 18. The coefficient of variation of some of the other normal organs of the body are: thyroid, 45; spleen, 38; thymus, 33; heart, 18; kidney, 17; liver, 15; brain, 8 (22), (23). Thus, while the whole hypophysis has a variability about like that of heart, kidney and liver, pars intermedia is much more variable than even such variable organs as the thyroid, spleen and thymus.

*Relative weight of pars intermedia with reference to the entire hypophysis and the epithelial portion only.* The mean and extreme percentages of the entire hypophysis (without capsule) which pars intermedia represents are listed in the first three columns of table 1.

TABLE 1

Relative weight of the different parts and of total pars intermedia as percentage of the entire hypophysis (without capsule) and as percentage of the glandular (epithelial), portion only; 111 normal male human adults

Components of Pars Intermedia	Per Cent of Entire Hypophysis			Per Cent of Glandular Portion		
	Minimum	Maximum	Mean	Minimum	Maximum	Mean
Parenchyma. .	13	3 6	9	17	4 8	1 1
Colloid... ..	02	10 4	1 2	02	11 3	1 6
Total. .. ....	.26	10 6	2.1	31	11 5	2 7

In order to make direct comparisons with the relative weights given for animals and human newborns, the data have also been computed as percentage of the glandular or epithelial portion of the hypophysis as shown in the last three columns of table 1. The mean value of the parenchyma in round numbers is 1 per cent (ranging from about .2 to nearly 5 per cent). This is about

2/5 of the percentage found in the newborn. But since the epithelial portion of the gland (and in fact the entire hypophysis) has increased about 5 times from birth to maturity, it follows that the absolute amount of epithelial tissue in pars intermedia has on the average actually doubled in weight during childhood.

If the colloid is reckoned as part of pars intermedia, then it constitutes essentially the same percentage in the adult as in the newborn with reference to both the hypophysis as a whole (2.1 per cent) and its glandular portion only (2.7 per cent).

In comparison with animals, the mean value for the parenchyma of the human pars intermedia constitutes about one-fifth as large a proportion of the epithelial portion of the hypophysis as the smallest mean value found in animals so far investigated quantitatively. If colloid is added, pars intermedia is about one-half as large a proportion of the gland as the minimal values in animals. As far as mean values are concerned, there should then be no serious objection to regarding this part of the hypophysis as being just as important to man as it is to some animals; but the minimum proportion (less than .2 per cent of the glandular part or, as shown in table 4, about .5 mgm. in actual weight) represents such a small mass of tissue that it is not strange to find that some investigators have regarded it as rudimentary. The percentage which this minimal weight con-

TABLE 2

Mean absolute weights (with the probable error) of pars intermedia, according to stature; 109 normal male human adults.

Stature cm.	No. of Cases	Parenchyma mgm.	Colloid mgm.	Parenchyma and Colloid Combined mgm.
152-170	43	4.1 ± .33	7.5 ± 1.04	11.6 ± 1.04
171-175	33	4.6 ± .54	6.9 ± 1.02	11.7 ± 1.18
176-192	33	5.1 ± .80	4.6 ± .70	9.8 ± 1.02

stitutes of a 70 kilogram body is in round numbers .000001 per cent. If it were in the form of a cube, it would measure .8 mm. each way. These small magnitudes ought to be kept in mind in any serious discussion of the rôle played by this part of the hypophysis.

*Relation of pars intermedia to stature.* The weight of the whole hypophysis is on the average noticeably greater in taller

individuals (21). The data on pars intermedia in this regard are shown in table 2. The 109 individuals with a record of body length have been divided into three groups according to stature. One group of 33 cases consists of those near the average in stature, leaving 43 that are distinctly below the average and 33 that are distinctly above. The parenchyma seems to increase slightly with an increase in stature, while colloid seems to decrease. However, the difference between any two groups is small and statistically not significant, as is shown in table 3. In the last column of the table the difference between groups compared has been divided by the probable error of the difference. To be

TABLE 3

Differences in the weight of pars intermedia of different stature groups and the significance of these differences

Structure	Difference Between Means	Probable Error of Difference	Ratio of Difference to Probable Error
152-170 compared with 171-175			
Parenchyma .	7	63	1 1
Colloid	6	1 46	4
171-175 compared with 176-192			
Parenchyma	3	81	4
Colloid	2 3	1 24	1 8
152-170 compared with 176-192			
Parenchyma	1 0	68	1 5
Colloid	2 9	1 25	2 3

statistically significant the resulting figure should be at least three; *i. e.*, in order to be fairly sure that the difference between two means is not due to mere chance in random sampling brought about by the limited number of cases involved and the degree of individual variation, the difference should be at least three times as great as the probable error of the difference. The formula for the probable error of the difference is

$$\sqrt{(PEa)^2 + (PEb)^2}$$

where PEa is the probable error of one of the means and PEb is the probable error of the other. A similar analysis shows that it is chiefly the anterior lobe that is responsible for the larger

hypophysis in taller men. The data supporting this statement will be available in the near future.

*Relation of pars intermedia to age.* The literature contains many statements on the change which pars intermedia undergoes

TABLE 4

Weight of parenchyma (epithellum) of pars intermedia, with the probable error of the mean, according to age; 111 normal male human adults.

Age, Years	No. of Cases	Minimum mgm.	Maximum mgm.	Median mgm.	Mean and Probable Error mgm.
20-30	17	9	11.5	2.0	2.9±.55
30-40	19	1 1	11.8	3.2	4.1±.60
40-50	28	.8	20.1	3.2	4.5±.60
50-60	25	.5	18.9	3.7	4.8±.56
60-76	22	8	17.3	1 1	5.6±.72
20-76	111	.5	20.1	3.1	4.6±.28

with advancing years. Thus Lucien (24), who studied 20 glands from 65 to 83 years old, considers it normally different histologically in the aged. The most common statement is that there is an increase in the invasion of epithelial cells into the nervous lobe in older individuals. An increase in the amount of colloid with age is also repeatedly mentioned. No test of the accuracy

TABLE 5

Differences in the weight of the parenchyma (epithellum) of pars intermedia of the different age groups and the significance of these differences.

Groups Compared	Difference Between Means	Probable Error of Difference	Ratio of Difference to Probable Error
20-30 and 30-40.	1 2	.81	1.5
30-40 and 40-50.	4	.85	.5
40-50 and 50-60....	3	.82	.4
50-60 and 60-76....	8	.91	.9
20-30 and 60-76..	2 7	.91	3.0

of these observations seems to have been made. General inspection may lead to erroneous conclusions where there is much individual variation.

The results of the quantitative method here employed are shown in table 4, which includes the mean values and their probable error together with the minimum, maximum and median weights according to 10-year intervals and for the entire series of 111 cases. Due to the positive skewness (towards the

low values) of the curve of distribution (figure 8), the median is in all cases distinctly smaller than the mean. Both the median and the mean increase regularly, though only slightly, with age, and thus seem to support general observations. If the significance of the differences is tested statistically, as already ex-

TABLE 6

Weight of the colloid associated with pairs intermedia, according to age; 111 normal male human adults

Age, Years	No of Cases	Minimum mgm	Maximum mgm	Median mgm	Mean and Probable Error mgm
20-30	17	1	51 1	2 9	8 5 ± 2 36
30-40	19	2	24 2	3 2	5 0 ± 94
40-50	28	1	35 8	3 8	6 6 ± 1 00
50-60	25	2	33 1	3 6	5 6 ± 93
60-76	22	6	33 1	3 4	6 3 ± 1 21
20-76	111	1	51 1	3 3	6 3 ± 55

plained, it is found (table 5) that the difference is too small, considering the relatively large probable error, to be actual proof that an increase occurs within a period of 10 years. When the youngest group is compared with the oldest group, the ratio of the difference to the probable error of the difference is 3, which is fairly good proof that there is an increase over a long period of years.

TABLE 7

Combined weight of the parenchyma and colloid of pairs intermedia, according to age; 111 normal male human adults

Age, Years	No of Cases	Minimum mgm	Maximum mgm	Median mgm	Mean and Probable Error mgm
20-30	17	1 3	52 0	5 5	11 4 ± 2 33
30-40	19	1 6	29 1	7 7	9 1 ± 1 03
40-50	28	1 3	37 9	7 8	11 4 ± 1 13
50-60	25	1 3	43 0	8 6	10 0 ± 1 21
60-76	22	2 0	38 6	8 2	12 0 ± 1 51
20-76	111	1 3	52 0	7 7	10 8 ± 62

In table 6 are recorded the data on the weight of the colloid by 10-year intervals. There is no proof here of any increase with age.

Finally, the combined weight of colloid and epithelium is shown in table 7, which indicates no significant correlation with age.

## SUMMARY

While there are those who discuss the significance of pars intermedia of man as if it were of considerable importance, a number of investigators, especially in recent years, doubt the existence of a true functional pars intermedia in adult man, and consider the epithelial tissue in that region of the mature human hypophysis as a rudimentary structure or as an extension of the anterior lobe. In view of the uncertainty regarding the specific function of this structure, especially in man, it appears best to retain the name "pars intermedia" for this part of the human gland, and to tentatively assume that it is homologous with pars intermedia of animals.

The general features of the changes in pars intermedia from the late fetal stage to the adult are described and illustrated with photographs.

Quantitative data on the relative size of pars intermedia to the epithelial portion of the hypophysis of various animals are reviewed. The mean values run as high as 25 per cent (in frogs) to as low as 5 per cent (in the woodchuck).

In the human newborn pars intermedia represents about 2.5 per cent of the epithelial portion of the hypophysis.

Data on the absolute and relative weight of pars intermedia of 111 normal male human adults (nearly all from cases of sudden accidental death) are presented with the view of giving a concrete idea of the variability and the exceedingly small amount of tissue that it may represent in some healthy individuals.

The epithelial portion (parenchyma) of pars intermedia was found to average .9 per cent of the whole hypophysis, varying from .13 per cent to 3.6 per cent. As percentage of the glandular portion of the hypophysis the corresponding figures are: average, 1.1 per cent; minimum, .17 per cent; maximum, 4.8 per cent. This is about  $\frac{2}{5}$  of the proportion found in the newborn.

The colloid associated with the intermediate region of the hypophysis averaged 1.2 per cent of the entire hypophysis, the minimum being .02 per cent and the maximum being 10.4 per cent. As percentage of the epithelial portion of the hypophysis, the corresponding figures are: average, 1.6 per cent; minimum, .02 per cent; maximum, 11.3 per cent.



The weight of the epithelium of pars intermedia averaged 4.6 mgm. (about twice the amount found in the newborn), varying from .5 mgm. to 20.1 mgm., the coefficient of variation being 94.

The weight of the colloid averaged 6.3 mgm, varying from .1 mgm. to 51.1 mgm., the coefficient of variation being 137.

The combined weight of the epithelium and colloid averaged 10.8 mgm., varying from 1.3 mgm. to 52.0 mgm., the coefficient of variation being 89. This means that pars intermedia, whether the colloid is included or not, is probably the most variable organ in the body, if it is a special organ.

The distribution curves for both portions of pars intermedia are so skewed toward the lower weights that the median values are from 29 to 48 per cent smaller than the mean (average) values given above. The median for the epithelium is 3.1 mgm.; for the colloid, 3.3 mgm., and for the two combined, 7.7 mgm. These probably represent a truer measure of the central tendency than the mean or arithmetic average.

The minimal weight (.5 mgm) of the epithelium of pars intermedia represents a mass no larger than a cube .8 mm. in dimensions, while the average (4.6 mgm.) would make a cube slightly less than 1.7 mm. in size.

The epithelium of pars intermedia of the adult seems to gradually increase with age. Statistically the proof is significant only when those under 30 years of age are compared with those over 60 years.

There is no evidence that the colloid in the region of pars intermedia increases with age in adults.

There is no significant correlation between stature and weight of pars intermedia.

There is no correlation between the amount of epithelium and amount of colloid in pars intermedia.

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## ESTROGEN, A NEW SEX HORMONE: ITS CLINICAL USE, WITH CASE REPORTS\*

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For a long period after the introduction of ovarian substances into medicine, the therapeutic results were uncertain. Glandular products heretofore, not questioning their pureness or exact site of origin or method of extraction, had to depend solely upon empirical testing for estimate of their potency. This is in contrast to drugs like digitalis and belladonna, for which we have a definite biological means of assay and are certain of the exact potency for a given dose. Faulty methods of manufacturing were primarily responsible, as there were no analytical methods for assaying these glandular products before placing them on the market for use in medicine. Estrogen, an extract of human placenta containing ovarian hormone will be presented as an illustration of a glandular product that has been assayed by definite biological methods.

The demonstration by Stockard and Papanicolaou of "the existence of a typical estrus cycle in the guinea pig, with a study of the histological and physiological changes," gave the basis for an assay of ovarian activity which has in ten years contributed more to our knowledge of ovarian hormone than all preceding research. These authors devised a biological test in which castrated mice are used to determine the presence of the sex hormone in the circulating blood. The test consists of a study of the vaginal spreads stained with a one per cent aqueous solution of thioin at twenty-four, forty-eight and sixty hours after the injections of the sex hormone and noting the character of the cells. A positive smear, which signifies the presence of the sex hormone in the circulating blood, that is one mouse unit, consists of a great preponderance of non-nucleated squamous scales, possibly some nucleated vaginal epithelial cells, but no leukocytes. This is the picture corresponding to that of normal oestrus in mice.

\* Read before the Section of Medicine, San Francisco Medical Society, January 3, 1923.

By means of this biological test the Allen-Doisy follicular hormone has been studied, its estrus stimulating effects ascertained, the site of its production discovered and ovarian products containing it standardized. Using this method of assay, Frank and Goldberger, Gustavson and Weyerts have demonstrated the presence of, and extracted the hormone from, the blood of the sow and human female.

Furthermore, it has been demonstrated that the functional mechanism of the menstrual process may be markedly influenced by the administration of substances derived from the two sources in the ovary, the follicular fluid and the corpus luteum, each of which has its specific hormone, which is elaborated at the time of puberty.

The cyclic phenomenon, estrus, occurring in the female, particularly in the lower orders, has been shown with reasonable certainty to be due to a hormone found principally in the follicular fluid of the matured Graafian follicle. Allen and Doisy extracted this hormone from follicular fluid and induced estrus in castrated female rats. This principle is used in assaying the activity of such preparations. They found it contained in preparations of placenta and in ovaries, from which the liquor folliculi had been removed, as well as in the liquor folliculi itself and corpus luteum.

Frank and Goldberger have shown that the follicular hormone progressively increases in concentration in the blood of the normal non-pregnant human female for a period of from ten to fifteen days before the onset of menstruation, disappearing at that time from the general circulation and appearing in the menstrual blood. The attainment of the maximum concentration of the hormone corresponds with the onset of menstruation and suggests that it induces it. In pregnant women the maximum concentration corresponds with the beginning of labor.

Besides this estrus inducing follicular hormone, Papanicolaou has isolated a luteal hormone which represses estrus and menstruation and accounts for the inhibiting action of the persistent corpus luteum in pregnancy. In the non-pregnant female this hormone of the corpus luteum may by its abnormally excessive production and persistence so diminish the effect of the follicular hormone as to give rise to amenorrhea.

Both before and following the development of the biological test many tissue extracts were investigated. One of the striking results of research of this kind was the demonstration by Herrmann of the follicular estrus producing hormone in the placenta. This work has been verified by such workers as Aschner, Allen and Doisy and Frank and Gustavson. Two theories are proposed to account for the presence of this estrus inciting hormone in the placenta: one that it is secreted by the placenta and the other that the placenta extracts the hormone from the blood. The latter theory seems the more probable, for Parkes and Belterby point out that estrus never occurs during normal pregnancy and that estrus artificially produced in pregnant animals by the injection of follicular hormone causes abortion and reabsorption.

The fact that corpus luteum is evidently able to secrete both hormones, the estrus inciting sex hormone and the luteal inhibiting hormone has not received general recognition. However, Frank, Bonham and Gustavson have shown that the female sex hormone, whether obtained from follicle fluid, corpus luteum or placenta, can be freed of all nitrogen, phosphorus, cholesterol and cholesterol reactions; and that from whatever source derived, it shows the same chemical properties and composition and gives a similar reaction on the contraction rate of the isolated uterus of the rat. Doisy corroborates this statement.

Using the biological test and method of assay prescribed by Allen and Doisy, the research department of one of our larger pharmaceutical houses at first isolated a product called Estron, which was an extract of the fluid obtained from the follicles of hog ovaries, no other product of the ovary being used. They apparently had a great deal of difficulty in collecting and standardizing this product for its physiological potency, and have developed in its place Estrogen, which has the same physiological properties but has the advantage over Estron in that it can be prepared on a practical basis with a greater potency as measured by the rat unit method of standardization.

Estrogen is a colloidal solution of human placental extract containing ovarian hormone. It is of the emulsoid type, with an opalescent appearance. Upon being allowed to stand, certain of the elements may separate, but they can be again emulsified by

shaking without any impairment of activity. It is intended for subcutaneous injection and not for intravenous use.

Chemically, each cubic centimeter was found to show:	
Total solids.....	2.75 milligrams
Total nitrogen.....	0.065 milligrams
Amino-Nitrogens.....	0.018 milligrams
Biuret test.....	Negative
Hydrogen ion concentration.....	5.5 to 6.0

The above values will vary with different lots, because the basis of standardization is physiological activity and not content of solids. One cubic centimeter represents from five to ten cc. of fresh follicular fluid.

Typical estrus has been produced in ovariectomized rats by subcutaneous injections of this extract. The effect is made use of in standardization of the product. They have adopted for the unit of potency the "Rat Unit," originally proposed by Allen and Doisy. One rat unit is the minimum amount which will produce estrus in an ovariectomized rat of 140 grams. Eight injections are given, four daily, for two days, estrus being determined by examining the cell forms found in the vaginal smear taken from the rats on the third and fourth days of the test. Estrogen is a sterile aqueous solution, and has been found to be non-toxic even in enormous doses, nor does it give signs of protein reaction.

Estrogen is suggested especially for use in functional amenorrhea, the subjective disturbance of either natural or artificial menopause, sexual frigidity, delayed puberty, lack of development of the secondary sex characteristics, and in some cases of mental depression.

The proper dose and interval between injections of Estrogen have not yet been definitely determined. Based upon physiological research work, it is suggested that doses of one to two cc. of Estrogen be administered daily for six or eight days, theoretically a few days prior to the expected date of menstruation. No further treatment is suggested after the administration of a series of injections until the next menstrual epoch. Subsequent treatment will of course depend upon the response obtained. It may be necessary to continue this plan of treatment, increasing the size or interval of dose as indicated. Estrogen is fur-

nished for experimental purposes in one cc. ampoules, packages of twelve.

### CASE REPORTS

I have had the opportunity of working with Estrogen since January, 1927, and have had under my observation twelve cases, demonstrating vaso-motor and nervous manifestations, the result of scanty or absent menstruation, and submit herewith six typical case reports.

**CASE 1:** Mrs. J. Mc., age 47. For the past five years the patient had been troubled with irregular menses associated with a burning sensation on top of the head, marked nervousness and pains in the back and legs. General physical and pelvic examinations were negative. She was treated for menopause with corpus luteum extract (5 grains) for a period of one year, with only slight improvement. At the menstruation period in January, 1927, the patient came in with marked aggravation of symptoms and was given a course of eight injections of Estrogen (1 cc.) intramuscularly every other day, with almost immediate relief of symptoms, and when last seen in December, 1927, had had no recurrence.

**CASE 2:** Mrs. V. H., age 42. Menses stopped at the age of forty and she had since been troubled with severe occipital headaches, nervousness, hot and cold flushes. There was no operative history. The patient had been treated with Varium (5 grains) three times daily, orally, without relief. She was given a course of eight injections of Estrogen, one every other day, with excellent results, but would get a recurrence of symptoms when the treatment was stopped.

**CASE 3:** Mrs. H. C. B., aged 54. The menses were stopped for the past eight years. The patient had since been troubled with severe hot and cold flushes, increase in weight, periodic occurrence of wheal-like rash, severe attacks of nausea, vomiting and fainting spells. Her condition was relieved by Hormonotone with Pituitary Extract during 1925 and 1926, and this last year the attacks have been controlled by Estrogen (1 cc.) at weekly intervals. The weight has become stabilized.

**CASE 4:** Mrs. N. A. R., aged 42, had been troubled with the appearance of irregular wheal-like areas about the face, neck and the upper chest, and an associated puffiness of the lids, swelling of the tongue and tightness in the chest. History was given of irregular, scanty menstruation, hot and cold flushes, nervousness and increase in weight. The condition was diagnosed as menopause with angio-neurotic edema. The nervous manifestations were relieved during the years 1925-1926 by giving Corpus Luteum Extract (1 cc.) intravenously at weekly intervals, but the swellings would recur. In January, 1927, Estrogen (1 cc.) was given intramuscularly with relief of hot and cold flushes and swellings. Menses stopped and the patient later developed signs of broncho-spasm. This patient belongs to a hypersensitive group.

**CASE 5:** Mrs. W. C., age 34. There was a history of a pelvic operation seven years ago, and the patient had since had scanty menstruation, associated with severe cramping pains in the right lower abdomen and excruciating occipital headaches, causing her to be bedridden. There were also hot and cold flushes and increase in weight. Prior to the present observation the patient was studied for foci of infection. The eyes were refracted. The Wassermann and pelvic examinations were negative. There was no history of migraine in the family. The condition was diagnosed as headaches due to ovarian deficiency, and has been relieved this last year by giving Estrogen (1 cc.) intramuscularly for three days prior to and up to beginning of menstruation. The patient has since been able to work throughout her periods, headaches are practically gone, and she required no treatment for the past three months.

**CASE 6:** Mrs. G. R., age 26. Menstruation started at the age of fifteen, was always irregular, often skipping several months, and was very scant, with barely more than a one day flow. Associated with this the patient had asthmatic attacks and fainting spells, especially marked at the time of the periods. In January, 1927, the patient was given a treatment of Estrogen, receiving injections once weekly and one injection at the start of menstruation. The nervousness and fainting spells were lessened and in September, 1927, she had a menstrual flow that lasted two days and was more profuse than usual. The patient was well for the following two months and then left for New Zealand. A report from her indicated that her asthma is worse, but she makes no mention of the character of the periods.

## SUMMARY

1. A biological test and method of assay has been introduced and established for the preparation of glandular products—particularly those relating to ovarian activity.

2. Estrogen is a biologically assayed product of human placenta containing ovarian hormone.

3. Estrogen has been found clinically in six cases to relieve the nervous functional manifestations of ovarian deficiency.

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# THE EFFECT OF ADRENALIN ON SUGAR METABOLISM

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According to most investigators (1) adrenalin increases heat production and raises the respiratory quotient, thus indicating an increase in sugar metabolism. The object of this investigation was to determine directly the effect of adrenalin on sugar metabolism. Practically all the work that has been carried out with adrenalin has been done on the mammal with its various organs and glands of internal secretion where the situation is very complex. In this investigation we have attempted to simplify matters by using single celled animals and adding the adrenalin directly to the sugar solutions containing these animal cells and studying the effect on the rate of sugar utilization. The animal cell used was *Paramecium caudatum*. The paramecia were raised in great numbers on an infusion of alfalfa, pond lily leaves, and lake water. They were collected and washed free of debris by the use of a small centrifugalizing machine. The centrifugalizing tubes were graduated in cubic centimeters, so the paramecia were measured as they were collected. Sugar determinations were made according to the method of Benedict. Air was kept bubbling through the liquid containing the paramecia to insure an adequate supply of oxygen.

The following is the description of a typical experiment. Forty cubic centimeters of paramecia were collected and measured as described above. These were added to 800 cc. of aerated lake water and 800 mgm. of dextrose was dissolved in the liquid. This 800 cc. batch of paramecia-sugar preparation was divided into eight portions of 100 cc. each. The 100 cc. portions were introduced into sedimentation glasses and air was bubbled through them. To one portion 1 cc. of a 1 to 1000 adrenalin chloride solution was added making a dilution of 1 to 100,000

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of adrenalin. Similarly quantities of adrenalin were added to the other 100 cc. sugar-paramecia preparations sufficient to make the dilutions indicated in Fig. 1. One portion to which no adrenalin was added served for control. Sugar determinations were made immediately and subsequently at intervals. It will be seen in Fig. 1 that the control used 39 per cent of the sugar in twelve hours; that relatively strong solutions of adrenalin, 1 to 100,000 and 1 to 200,000 decreased sugar metabolism, but the weaker solutions 1 to 1,000,000, 1 to 24,000,000 and 1 to 40,000,000 increased it while still weaker solutions, 1 to

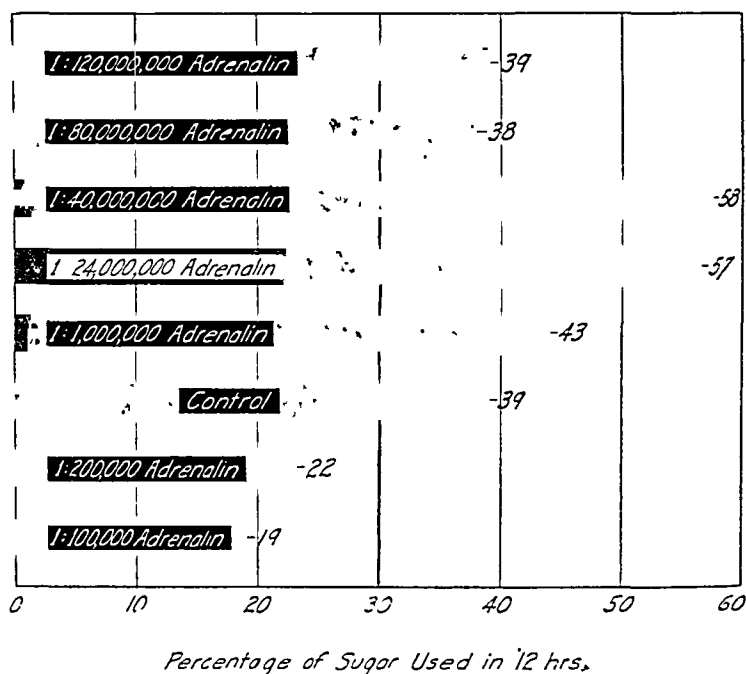


Fig. 1. Chart showing the effect of various amounts of adrenalin on the rate of sugar utilization by paramecium.

80,000,000 and 1 to 120,000,000 had no effect. The decrease in sugar metabolism brought about by the stronger solutions is attributed to the so-called toxic action of adrenalin while the weakest solutions were ineffective because of their great dilution.

During the past year and a half we have carried out a great number of experiments similar to the preceding with com-

parable results. It was observed that the adrenalin in the various portions of the 100 cc. paramecia-sugar preparations was oxidized during the experiments as was indicated by the fact that the preparations became reddish in appearance. The doses of adrenalin were accordingly repeated every hour to offset this destruction and to insure, as far as we could, the presence of adrenalin in the preparations at all times.

Hoskins (2) found that different size doses of adrenalin had different effects on blood pressure just as we find to be the case on sugar metabolism. He found that small doses of adrenalin produced a fall in blood pressure and large doses a rise, whereas, we find small doses, if large enough to be effective, increase sugar metabolism and large doses decrease it.

Two questions might be raised in this connection: First, did the paramecia use the sugar in these experiments, or was it yeast or bacteria? Second, will these results obtained with paramecium hold for the higher animals and man? The first question can be answered by stating that we have found that if the paramecia be removed by centrifugalization during an experiment, sugar utilization ceases. The second question can be answered only indirectly. We (3) have found that paramecia use all three of the simple sugars just as do the higher animals and that they use dextrose and levulose more rapidly than galactose, again resembling the higher animals and man. It was also found that insulin increased the rate of utilization of sugar by paramecium just as it does in man.

#### SUMMARY

Experiments were carried out, adding adrenalin to cultures of paramecia in dextrose solution. It was found that small amounts of adrenalin increase sugar metabolism, while large amounts decrease it.

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# ON THE GRADED RELATION BETWEEN THE INTENSITY OF HORMONE ACTION AND THE CHARACTER OF THE RECIPIENT TISSUE

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In the following paper it is not our desire to give a detailed description of the sexual cycle of the guinea-pig. Previous publications (1) have dealt with various phases of this problem, and we intend to return to some questions relating to cyclic changes also in a future publication. In this paper we wish to draw attention to a condition observed by us in the sexual cycle of the guinea-pig, the significance of which is, however, not restricted to the sexual cycle, but which applies to the relation in general between the hormone and the substance on which it acts. Inasmuch as our conclusions are based largely on a study of the cyclic changes which occur in the cervix of the guinea-pig, it will be necessary first to give a brief description of the cervix uteri of this animal.

We may divide the cervix into three parts: (1) The vaginal cervix, or the cervical canal; this is a continuation of the vagina and represents a fairly straight canal. On the whole it behaves like the vagina, but the processes which take place in the latter are somewhat moderated here. The portio uteri which joins the vagina to the cervical canal behaves very similarly to the vagina. (2) The middle cervix, usually represented by a widening of the canal, the lumen of which is largely filled with branched papillæ. (3) The uterine cervix, the lining of which in certain respects begins to resemble the uterine mucosa; however, the epithelium of this part is of a vacuolar character similar to that found also in the middle cervix, and under certain conditions even in the vagina, although in the latter place, even if the epithelium is vacuolar, it usually has some distinctive characteristics of its own. On the other hand, scattered areas of cylindrical, vacuolar epithelium, resembling the epithelium of the uterine cervix, may also be found in the uterine mucosa at various periods.

The greater similarity between uterine cervix and uterus is still more strongly accentuated through the fact that in the uterine cervix the formation of glands, similar to those found in the uterus, begins. In the medium cervix we find, corresponding to these glands, epithelial invaginations situated between the papillæ and covered with an epithelium which is less coarsely vacuolar than the epithelium lining the papillæ. In the vaginal cervix there is, under some conditions, below the cylindrical layer a single layer of cuboidal or flat cells, while in other cases there may be several layers of the latter cells, the findings varying with the amount of growth hormone acting on the epithelium. In the middle and uterine cervix also there may be, at certain periods and in certain places, a layer of flat cells below the cylindrical layer; but in other places this may be lacking. In these parts as well the variations which occur in the character of the epithelium are in accordance with the period of the sexual cycle at which we observe the tissue, and also in accordance with the quantity of growth hormone which has been active.

The connective tissue in the different parts of the cervix also shows transitions between the connective tissue of the vagina and that of the uterus. Thus, it is fibrous in the vagina, more or less cellular in the uterine mucosa, and intermediate in character in the cervix; here it is more fibrillar than in the uterus, but not quite so fibrous as in the vagina. A greater number of cells and a diminution in the fibrous character of the connective tissue are found especially in the uterine cervix and in the papillary part of the middle cervix. On the whole, the cervical connective tissue resembles the connective tissue of the vagina more perhaps than that of the uterus; but, as stated, a certain gradation in its character in the different parts of the cervix is noticeable.

We shall now briefly describe the effects of the hormone action on the various parts of this canal at various stages of the sexual cycle. It is our purpose rather to define the principal changes, as far as they serve to illustrate our main conclusion, than to give a detailed description of the cycle.

A. *The stage preceding ovulation.* This is the period during which an active proliferation is taking place in the vagina which leads to the production of a well developed keratinized squamous

epithelium. A very marked mitotic proliferation begins in the lowest row of the epithelium, and it progresses until the highest layers have become transformed into keratin. When a thick layer of keratin has thus been produced, active mitotic division may at first still continue in the vaginal epithelium, but soon mitoses diminish in number. It is only the lowest layer of cells which proliferates in this way and forms keratin; the upper cylindrical layer remains passive, being merely raised up by the underlying squamous epithelium. Simultaneously with the proliferation of the vagina, there begins also a proliferation of the vaginal portion of the cervix, but it is less marked than in the vagina. Mitoses occur in the low cuboidal epithelium which rests on the connective tissue of the vaginal and also of the middle cervix; they may also be found in the cylindrical vacuolar epithelium which lies on top of the lower epithelium, or which may be in direct contact with the connective tissue. However, the number of cell rows is less in the vaginal cervix than in the vagina. The cuboidal epithelium at this period extends also into the uterine cervix, although there may be places here where it is lacking. Mitoses may also occur in the glands of the uterine cervix.

As far as the connective tissue is concerned, it becomes in the uterine cervix somewhat more cellular and less fibrous than it is in the vagina. However, in the uterus the connective tissue is still more cellular than in the uterine cervix.

When much keratin is produced in the vagina, oestrus changes may be noticeable in the uterus, namely, a greater height of the cells in the surface epithelium with mitoses, which extend also to the upper gland ducts. The mitoses, however, occur only in those areas of the epithelium where the cells are more solid and cuboidal, whereas the areas of higher cylindrical, more vacuolar epithelium, resembling that of the cervix, do not usually undergo mitotic proliferation. Underneath these latter areas a more edematous condition of the connective tissue may be noticeable and some collections of lymphocytes may also be found. The edematous condition of the connective tissue seems to favor the formation of papillæ in the uterine mucosa. As we observed previously, the mammary gland, as a rule, is proliferating at this period of the cycle.

B. *The stage directly following ovulation.* During this period the proliferation in the vagina decreases very markedly, and, in some cases, it may apparently be lacking. However, it seems that in certain places, especially in the region near the cervix, the number of mitoses remains still greater than elsewhere in the vagina. The keratin is cast off at this time, either at the beginning of the period or a little later, and with it the layer of cylindrical vacuolar cells lying on top of the keratin. These cylindrical cells, and especially their nuclei, now appear shrunken, owing to the insufficient supply of oxygen which they have received. Probably as the result of the diminished proliferation at this period, the mass production of keratin in the upper layers of the epithelium has ceased and we begin to notice instead a hyalinization or keratinization of individual epithelial cells, likewise situated in the upper layers of the epithelium; they also are insufficiently supplied with oxygen or other food stuffs. The gradual desquamation of these cells underneath the sheets of keratin may account for the fact that the latter is cast off in toto. As the result of the stage of proliferation in the preceding period, papillary processes of the vaginal epithelium, reaching into the connective tissue have developed, and in the center of some of these a formation of keratinizing epithelial pearls may take place. Lymphocytes and also polymorphonuclear leucocytes, unrestrained by the protective layer of keratin, migrate at various points into the lumen of the vagina; they collect here and may be observed, together with desquamated particles of keratin and with phagocytic cells, which latter take up the leucocytes.

In the cervix, conditions are transitional between those in the vagina and in the uterus. In the portio the epithelium is of about the same character as in the vagina, although the squamous epithelium may be slightly lower in the former. In the vaginal cervix, the cervical duct, proliferation has also taken place and mitoses may still be found, even in cases in which they are lacking or very rare in the vagina. Here, too, proliferation has led to the formation of keratin, on which the layer of cylindrical epithelium rests. A part of the keratin, with cylindrical epithelium, may be cast off, especially in the lower (distal) part of the cervical canal, whereas in the proximal portion which approaches the middle cervix the keratin may still be found adherent to the



squamous epithelium, and the cylindrical epithelium, on its part, is here still adherent to the keratin. In those places, where the keratin is adherent, the squamous epithelium is less thick and the keratin thus has developed somewhat later than in the more distal portion of the sex duct, which accounts for the fact that the processes are less advanced in these more proximal areas. The keratin formation may in some cases reach even into the beginning of the middle cervix, the cavity which is filled with papillomatous formations, but here the keratin formation soon ceases; in other cases it extends merely into the vaginal cervix. At this stage we may also find here and there in the upper layer of the epithelium in the vaginal cervix, epithelial cells which hyalinize or undergo certain phases of keratinization. This process takes place instead of keratinization en masse, leading to the formation of sheets of keratin, which was observed in the preceding period. In the middle cervix the layers of squamous epithelium diminish in number, and on the top of the slender papillæ, in the dilated portion of the cervix, the squamous epithelium, underneath the cylindrical epithelium, may be lacking altogether or be very low, consisting merely of one or two rows of cuboidal or flat cells. Gradually the squamous epithelium may entirely disappear and the layer of cylindrical epithelium may rest directly on the connective tissue, a condition increasingly found the nearer we approach the uterus. But even in the uterine cervix there may be, in places, one or even two layers of flat epithelium below the cylindrical epithelium, individual variations existing in this respect.

The glands begin to develop in the uterine cervix, and in certain animals they may reach even into the adjoining margin of the middle cervix. Mitoses may occur in these glands, but on the whole they seem to be less frequent than in the uterine glands. Where the glands begin, the mucosa is usually somewhat richer in connective tissue cells, although it does not as yet attain the cellular condition which we find in the uterine mucosa proper. Lymphocytes may enter the epithelium of the cervix at various points; also polymorphonuclear leucocytes frequently migrate through the cervical mucosa, especially in places where there is no keratin to exert a protective effect. These leucocytes

may injure the cylindrical epithelium and cause or increase the vacuolization we find in these cells.

The great majority of the animals which we examined had not copulated, but in those animals in which copulation had taken place conditions were essentially similar to those found in the other group. However, in the former a vaginal plug developed and, following copulation, large masses of polymorphonuclear leucocytes migrated through the vaginal wall, where the keratin layer was lacking. Also in the portio of the cervix, leucocytes may invade and migrate through the epithelium in such large masses that the epithelium is destroyed in certain areas and ulcers may develop. On the whole, the leucocytic migration is more marked in the cervix than in the vagina. Small nodules of lymphocytes too are found in the cervical mucosa, and in the uterine cervix lymph vessels may here and there be filled with lymphocytes.

In the uterus we may find at this period high cylindrical epithelium in which mitotic activity is proceeding; mitoses are also found in the gland ducts where they enter the surface epithelium and are enlarged. There may also be a few mitoses in the connective tissue of the mucosa. Many polymorphonuclear leucocytes migrate through the epithelium and may injure it. Especially following copulation, polymorphonuclear leucocytes may exert a destructive effect on the epithelium and spermatozoa may be found in the gland fundi. Lymphocytes also migrate through the mucosa into the epithelium. Patches of mucoid epithelium, with a structure corresponding to that found in the uterine cervix, may be seen after the rupture of follicles. In the majority of cases mitoses are also found in the mammary gland at this period.

C. *The sex organs during the period from the first day following ovulation to the onset of the new cycle.* (1) *The vagina.* Soon after ovulation, as we have seen, the keratin is cast off and the proliferation of the epithelium almost ceases, or at least it becomes very slight. Accordingly mitoses may be absent, or, if present, they are not very numerous. They are found especially in the broad papillary processes, which the epithelium sends downward into the connective tissue, and they may also be more frequent in the region near the cervix. As a result of this diminution in epithelial proliferation and associated with it,

there is a corresponding diminution in the number of layers of squamous epithelium and a change in the character of degeneration in the upper layers of the epithelium. Both of these processes are merely an accentuation of the alterations which began in the period directly following ovulation. The number of cell rows which can be observed varies between one and three or four. Sometimes we find only a single layer of cuboidal or flat cells, covered by a layer of cuboidal or cylindrical cells in which individual cells have undergone hyalinization or a beginning keratinization. In other cases there are two or three layers of squamous epithelium, and on top again there is a layer in which cells hyalinize or keratinize. Especially following the sixth day, the epithelium may be very low. During this latter period mitoses apparently occur in the upper rows of the epithelial cells. Also some occasional amitoses are seen here. Instead of the formation of connected sheets of keratin, such as we find in the earlier period, we again observe merely processes of hyalinization, or perhaps of partial keratinization of individual cells in the upper row of the epithelium. These cells keep their nuclei during the degenerative processes and are then cast off as isolated, nucleated cells into the lumen of the vagina; but occasionally a row of upper cells may undergo these changes simultaneously and be cast off as a layer of nucleated cells. At other times we find merely a remnant of squamous epithelium deprived altogether of hyalinizing cells. The typical keratinization occurs only if we have to deal with a relatively rapid growth of epithelium, when, as a result of this active proliferation, the upper layers of cells are quickly raised up and thus removed from the source of oxygen supply and of food stuffs. If the distance between the vessels and the upper rows of the epithelium is quite short, and the process of raising up takes place slowly, a more incomplete necrobiotic change leading to hyalinization or partial keratinization of cells, which still keep their nuclei, takes place. As stated, in some cases merely some cuboidal or low cylindrical cells develop in the upper row which do not show any sign of hyalinization.

Towards the end of the sexual period, at about the fifteenth day or somewhat later, following ovulation, a new active proliferation in the vagina, leading to typical keratin formation, may set in. We have observed this event so far only after degen-

eration of the corpus luteum of the preceding cycle has begun. Whether it may occur also at a time when the corpus luteum of the preceding cycle is still functioning remains to be seen. It is the epithelium nearest the connective tissue which proliferates when the stimulus, emanating from the growth substance, reaches it. In consequence of this proliferation the upper cell row is raised passively and becomes the layer of cylindrical epithelium which we later find covering the squamous, keratinized epithelium.

Whereas in the first period of the cycle we find a migration through the epithelium, especially of the polymorphonuclear leucocytes, somewhat later the lymphocytes become prominent; they may invade the epithelium and cause localized injury of the epithelial cells. In addition, some nodules of lymphocytes may be found in the connective tissue beneath the layer of epithelium.

(2) *The cervix.* (a) *The vaginal and middle cervix.* As compared with the conditions which obtain during oestrus, we find in the vaginal cervix a diminution in the height of the squamous epithelium and in the number of rows of flat or low cuboidal cells which corresponds to that observed in the vagina; however, in accordance with the general rule stated, the number is smaller in the vaginal cervix than in the vagina. In addition there takes place a gradual lowering in the height of the squamous epithelium in the direction from vagina to middle cervix. Near the vagina there may still be several rows of epithelium, the upper layer being formed of cuboidal or low cylindrical cells in some of which, here and there, some hyaline changes may take place; but a little higher up in the vaginal cervix the width of the squamous epithelium decreases, until only one or two rows of flat cells are found, covered by a layer of well developed vacuolar cylindrical cells. At a still greater distance from the vagina, the flat cells, which are in appearance not unlike connective tissue cells and which are situated underneath the layer of cylindrical cells, disappear altogether and the layer of cylindrical vacuolar cells rests directly on the connective tissue. This condition prevails especially in the middle cervix, although even in this portion of the cervix there may in places appear a second layer of flatter cells below the cylindrical layer. Where processes are sent by the epithelium down into the connective tissue, and where some cells are pushed below others,

the appearance of squamous epithelium may be simulated. At other points an epithelial process may push laterally into the superficial layers of the connective tissue and may thus be separated from the surface epithelium by a thin strip of connective tissue.

As in the period preceding and directly following oestrus, there is also during the remainder of the sexual cycle a formation of papillæ, which is especially marked in the middle cervix, but which, in a less pronounced way, may begin already in the vaginal cervix. The papillæ in the cervical cavity are perhaps no longer as slender as they were at the time of oestrus, but again the epithelium at the top of the papillæ is more vacuolar, probably owing to the edematous condition of the papillæ. Also in the recesses between the papillæ the epithelium is now, as it was during the oestrus period, more solid than in other places, and it thus resembles the epithelium of the glands which develop near by in the uterine cervix. Mitoses are present in the cylindrical surface epithelium of the middle and also of the vaginal cervix, and in the epithelium of the recesses mitoses may likewise occur. In addition, there are found during this period in the middle cervix, underneath the epithelium of the papillæ, very large vacuolar cells, the character of which, whether they consist of connective tissue or of epithelial cells which were pushed downward into the subjacent layer of the connective tissue, is uncertain. As in the preceding period, polynuclear leucocytes and lymphocytes migrate into or through the epithelium and may injure it in places, and lymphocytes may also collect in the connective tissue underneath the epithelial layer.

(b) *The uterine cervix.* In the uterine cervix the structure becomes more similar to that of the uterus. We find here a single layer of cylindrical epithelium, which rests directly on the connective tissue, although in places a second layer of flat cells may appear below the surface layer. In the beginning of the uterine cervix there may be observed some solid invaginations of epithelium into the connective tissue, while further towards the uterus typical glands appear. The papillary formations, characteristic of the middle cervix, become here less prominent, and the connective tissue of the mucosa becomes somewhat richer in cells, although it is not yet as cellular as in the typical uterine

mucosa. Mitoses are found in the cylindrical epithelium of the uterine cervix as in other parts of the cylindrical epithelium covering the cervix; likewise in the short glands of the uterine cervix rare mitoses may be seen, but in some cases they are lacking in the glands of the cervix even at periods when they are present in the uterine glands. However, it is of special interest that the predecidual proliferation which takes place in connective tissue and vessels of the uterine mucosa, approximately from the third to the sixth day following ovulation, does not occur in the uterine cervix, except perhaps in a small border area directly adjoining the uterus.

*Uterus.* We have previously described in detail the changes which occur in the uterus and mammary gland in the course of the sexual cycle, and we refer therefore essentially to our previous descriptions (1). We may recapitulate the principal events, as follows: In the first three days following ovulation the uterine surface epithelium is high cylindrical, and in the first two days mitoses are found in it. Also some small islands of vacuolar cylindrical epithelium resembling the uterine cervix epithelium may occur. Mitoses are seen after one day in the upper gland ducts and after two or three days they may extend to the middle portion of the gland ducts, but the gland fundi are as yet small. While in the connective tissue and capillaries of the mucosa there may at first still be some mitotic activity remaining from the oestrus period, after two and three days only a few mitoses are seen in the connective tissue and vessels of the subepithelial zone, indicating thus the beginning of the lutein phase. At this period some hyperemia may appear and occasionally some small hemorrhages are seen in the mucosa. A very active predecidual proliferation takes place in the uterine mucosa on the fourth and fifth day; the mitoses extend now to the gland fundi; but accompanying the proliferation in the subepithelial tissue and in the glands three, four and five days following ovulation, the mitotic proliferation in the surface epithelium ceases. Gradually towards the fifth and sixth days the surface epithelium becomes low, cylindrical, and mitoses in the glands likewise now are rare or altogether lacking. After six days there may still be occasional mitoses in the mucosa, but soon afterwards they cease entirely and degenerative processes occur in the predecidual cell layer. The glands also become small. At eight to

ten days after oestrus some mitoses may appear in the surface epithelium. The connective tissue of the mucosa is now in a resting state. Toward the end of the cycle the epithelium, glands and mucosa again begin to assume the oestral condition.

From the third day following ovulation to the end of the cycle the mammary gland is on the whole quiescent, although some rare mitoses may be found occasionally, but with the new period of heat, a temporary proliferation of the gland sets in anew.

*Concerning the mechanism underlying the graded changes in the cervix.* We see, then, that the proliferation which takes place under the influence of the hormone given off by the ovary at the time of oestrus shows a graded intensity which decreases in the direction from vagina to uterus. These findings might possibly be interpreted by the assumption that the proliferating epithelium of the vagina is mechanically pushed in the direction towards the cervix and into the vaginal cervix, and that thus the appearance of a graded proliferative activity is simulated, whereas in reality such a gradation does not exist. It can, however, be shown that such an interpretation would be incorrect. The gradual decrease in the number of mitoses which can be observed in passing in the direction from vagina to uterus, and which corresponds to the gradation in proliferation, is unfavorable to such an interpretation, as is also the graded change in the behavior of the keratin, which in the vagina and near the vagina is cast off earlier than at points higher up in the vaginal cervix, where it still remains adherent at a time when it has been cast off in the more distal areas. However, it is possible to decide this question definitely by interrupting the connection between the vagina and the cervix or between parts of the upper and lower vaginal cervix by applying a tight-fitting ligature around either the upper vagina or the vaginal cervix; such a procedure precludes a movement of the epithelium from the vagina into the cervix. We have carried out such experiments in a number of cases and have found that under these conditions the graded intensity in proliferation in the vaginal-cervical tract persists. If, however, the thread is applied in the cervix, a localized production of keratin is noticeable directly around the thread. We may then conclude that the gradation in proliferative activity in the vagino-cervico-uterine tract actually exists and is not merely

simulated through a mechanical pushing upward of the vaginal epithelium.

The same gradation in intensity of proliferation, associated with transitional conditions in structure in this area, which we observed under the influence of the follicular hormone given off in the course of the normal cycle, we also observed under experimental conditions, after administering a series of injections of follicular extract in guinea-pigs, and thus producing the signs of oestrus. Under these circumstances we see the same gradual decreasing intensity in the growth processes with which are associated the transitions in structure that we find in the normal cycle.

However, not only during the period of the normal cycle, but also in various other conditions have we observed the same correspondence between the structure of the different areas of the vagino-cervico-uterine tract and the growth processes under the influence of hormones. Thus in both hysterectomized and pregnant animals we found a resting state throughout the tract and a relative lack of growth processes; the conditions found in immature guinea-pigs or in those which are undernourished likewise sustain our conclusions. The changes taking place in the sex tract under these latter conditions, in so far as they have not yet been discussed previously, will be treated in a subsequent publication.

#### DISCUSSION AND CONCLUSIONS

Our observations prove that growth substances act on adjacent tissues in a graded way. The same amount of growth substance circulating in the body fluids induces in neighboring cells a response of graded intensity. This gradation corresponds to and is correlated with a certain gradation in the structure of the organs concerned. Furthermore, the responses obtained experimentally are identical with those observed during the normal cycle; it would seem, therefore, that in both cases they are produced by the same growth substances. If we inject follicular hormone in effective quantity twice a day in guinea-pigs, we find the vaginal epithelium proliferates and actively produces keratin. In the uterus, on the other hand, the changes, as far as proliferative activity is concerned, are relatively slight. There may be some edema and congestion and, here and there, we may observe



a connective tissue cell in mitotic division. In the cervix which joins vagina to uterus the proliferative conditions as well as the structural features are transitional between those found in the two adjoining organs and there is moreover a graded reaction; the nearer the portion of the cervix to the vagina, the more it reacts like the vagina at a particular period, although the reaction is always quantitatively weaker, until it reaches the neighborhood of the uterus, when it begins to show an activity and a structure approaching those characteristic of the uterus. There are two factors which might be concerned in this result. In the first place, it is conceivable that the gradation in intensity of proliferation is due to a gradation in the amount of substance taken up by the adjoining tissues, and, secondly, it is conceivable, even in case the tissues have taken up the same amount of growth substance, that their structure would cause them to respond to the action of the growth substance with a different degree of proliferation. It is also possible that a combination of these two factors is effective, and this latter assumption has the greater degree of probability, because it appears likely that the same factor which renders a tissue more or less adjusted to a hormone regulates the amount of this substance which is anchored to that particular tissue.

This is, as far as we know, the first instance in which there has been observed a gradation in the intensity of reaction to the stimulus of a hormone, corresponding to a gradation in structure of the reacting tissues. In regard to the interaction between growth substances and tissues, we can in general distinguish between two kinds of the former, namely, (1) those acting from a distance, as when a substance given off by one organ acts on another organ. Thus the substances given off by the corpus luteum and the follicular substance represent such agents. (2) Contact substances, among which may be included the organizer substances of Spemann. In all cases in which hitherto growth and differentiation were produced by such substances, a certain tissue either responded or did not respond. Under certain conditions the response was less intense than under other conditions; but to our knowledge no gradation in the response of adjoining tissues has ever been observed in either of these sets of reactions, such as we have observed in the case of the cervix. However, a certain relation may exist between the facts described

by us and the observations of Child and Hyman. These authors have observed that, in general, during regeneration or embryonal development or even in fully developed organisms, the most actively growing parts or organisms are those which are at the same time most sensitive to the effects of a diminution in the amount of available oxygen supply; and that gradients exist in which these two properties, namely growth and sensitiveness, increase or decrease in a corresponding manner.

As to the relation between the character of the tissues which enter into combination with the hormone, and the effectiveness of the hormone action, we must consider especially the intermediate part of the system, namely, the cervix. The distal part of the cervix, the vaginal cervix, is similar in structure to the vagina; but it differs from the latter in its gradually decreasing ability to react to the growth stimulus given off by the ovarian hormone. In the adjoining intermediate zone of the cervix, the epithelium undergoes changes which render it more similar in structure and behavior to the epithelial lining in the uterine cervix and to a similar type of epithelium which may occur in isolated areas here and there in the uterus. As a preparation for the gland formation which begins in the uterine cervix, we find in the intermediate, transitional zone of the cervix the development of epithelial recesses or crypts in which the epithelium is more solid; at the same time the formative conditions which are active here lead to the more marked development of papillæ. As an indication of the relationship between the epithelium of the intermediate zone and the vaginal epithelium, we may still find a slightly greater tendency to proliferation in the beginning of the intermediate zone. This tendency, however, soon ceases and the epithelium becomes unresponsive to the formative stimulus of the follicular hormone, and in this respect it resembles the uterine epithelium.

On the other hand, neither the connective tissue of the proximal portion of the intermediate cervix nor that of the uterine cervix acquires the ability to react to the stimulus of the corpus luteum hormone in a manner similar to the characteristic reaction which we established in the uterine mucosa. While thus the connective tissue of the proximal portions of the cervix does not become identical in character with the corresponding tissue in the uterus, we observe corresponding to a gradation in the

properties of the epithelium, a gradation in the character of the connective tissue, a more fibrous connective tissue being co-ordinated with the squamous epithelium of vagina and the potentially squamous epithelium of the vaginal or distal portions of the cervix and a more cellular connective tissue with the cylindrical or cuboidal epithelium of the uterus or the proximal portion of the cervix. However, at no period of the sexual cycle does the connective tissue, even of the uterine cervix, become as cellular as the connective tissue of the uterus.

Whenever the proliferative stimulus, acting on a responsive tissue, reaches a sufficient intensity, a transformation takes place of cylindrical epithelium, beneath which there may be a layer of flat cells, into squamous epithelium. The structure and metabolism of this epithelium is of such a kind that if the proliferation is rapid and the upper rows of the epithelium are thus raised up within a short time and removed a considerable distance from the blood vessels, the oxygen and food stuffs, the cells affected in this way undergo *en masse* a degenerative change which leads to the production of keratin.

In the case of the vagino-cervico-uterine tract, the epithelium shows certain structural differences. But there exist finer differences between adjoining portions which it is not possible to discern by ordinary distinctions based on structural characteristics, and for such differences fine gradations in the reactions permit a differentiation, where mere morphological criteria are insufficient. Similarly, it is the proliferative reaction, on the part of the connective tissue of the mucosa, to the hormone of the corpus luteum which enables us to differentiate between the connective tissue cells of the uterine mucosa and connective tissue cells of the cervix, vagina, Fallopian tube and serosa, although ordinary structural criteria of differentiation are lacking.

#### SUMMARY

1. An analysis of the actions of growth hormones on the vagino-cervico-uterine tract reveals a graded reactivity of the tissue to the stimulating effect of the hormone in the direction from vagina to uterus. The graded intensity of proliferation thus established corresponds to gradations in the structure of the tissue. This is, as far as we know, the first observation of a gradation of hormone action on contiguous parts of a tissue; it

is presumably due to a graded degree of reactivity of the tissues to the hormones as well as to a graded ability of adjoining cells to combine with certain hormones.

2. There are, associated with the intensities of proliferation of the epithelium, graded rapidities and intensities of transformation into keratin of the upper epithelial layers which are farthest removed from the source of oxygen and other foodstuffs, the process leading to the production of sheets of keratin and to an early casting off of these layers in the region corresponding to the greatest proliferative energy, a hyalinization of isolated cells taking place in the region corresponding to a diminished growth energy.

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# THE IODINE CONTENT OF BLOOD IN ORDINARY GOITRES AND IN CRETINISM

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Since the adaptation of iodine determination, as described by Fellenberg and McClenden, interest has been stimulated in the determination of blood iodine content in man.

Veil and Sturm of Munich have contributed an excellent paper on the blood iodine content of human beings. Their work was done on normal and pathological individuals. They demonstrated the variability of iodine content under certain conditions; also the variability of blood iodine content in the same individual during summer and winter seasons, it being lower in the latter season.

That iodine is a constant and physiological element of the blood, is demonstrated by the fact that Veil and Sturm in the analysis of some 450 specimens found food iodine to be present in 100 per cent. The content in normal individuals is quite constant; also the variability of the different seasons. Besides many other pathological conditions, they also set forth the definite relation existing between blood iodine content in hypo- and hyper-thyroidism.

Taking a normal individual at late summer season and considering his iodine content at 13 milligrams per cent, they demonstrated that of the struma patient to be from 30 to 60 per cent lower than normal, showing only from 3 to 9 milligrams per cent, while in cases of Basedow's disease they found the content to be 21 to 70 milligrams per cent.

The contention that there is a definite relationship between the thyroid gland and iodine is substantiated to a certain extent by the experiments of Welch. His animal experiments were done at the Montana Agricultural College, Bozeman. Mon-

tana. In his conclusions he states that disturbance of function of the thyroid gland appears to be a cause of hairlessness in animals and that the enlarged thyroid glands are very deficient in iodine content. Iodine supplied to the female breeding stock during gestation is apparently effective as a preventative of goitre in the new born.

At the clinic of Bern it was thought that it would be of interest first to determine the iodine content of thyroid and peripheral venous blood, to ascertain whether or not a difference existed.

The method of determination employed was that of Fellenberg, under whose direction most of the following work was carried out in the laboratories of the Public Health Department of Bern.

In this paper, we shall not discuss the historical evolution begun by Robourdin in 1850, of the process of blood iodine determination, which has resulted in the present methods of Fellenberg and McClenden. This has been ably set forth in the papers of Veil, Sturm and Fellenberg. In this work the method of Fellenberg was followed precisely, and is but outlined as follows:

To 10 cc. of blood previously oxalated with 1 cc. of 2 per cent sodium oxalate solution, 1 gm. of KOH was added. This mixture was slowly ashed with constant stirring using the usual precautions not to overheat the same and drive off some of the iodine content. The ash was then mixed with 10 cc. of distilled water and filtered. The remaining residue was again burnt quite thoroughly, and to this was added the filtrate which was slowly heated to dryness, finally heating to a red glow. After cooling, extraction was begun with alcohol. Six drops of potash solution plus 2 cc. of dilute iodine free alcohol was added and thoroughly rubbed, pouring the solution off into a platinum dish. Extraction with undiluted alcohol was repeated twice. Placing six additional drops of potash solution into the platinum dish, it was then placed upon the water bath and slowly steamed to dryness. It was often found necessary to repeat extraction with alcohol a second time owing to the large amount of residue remaining after heating on the water bath.

Determination of the iodine content was now done by both the titration and colorimetric methods. The residue in the platinum dish was dissolved in 1 cc. of distilled water and poured into a small test tube, to which was added one drop of a solution of dilute  $\text{H}_2\text{SO}_4$  plus  $\text{Na}_2\text{NO}_3$ , setting free the iodine, and 0.02 cc. of chloroform; then shaking thoroughly for a qualitative determination. The red violet chloroform drop was then compared with known standards. Proceeding next to the determination by titration, the solution used for the colorimetric findings, plus two washings of the platinum dish, were placed in an Erlenmyer flask, adding a small amount, approximately 0.5 cc. of bromine water and boiling until completely oxidized;

then after adding a kernel of potassium iodide and a drop of starch solution as an indicator, titration was done with N/250  $\text{Na}_2\text{S}_2\text{O}_3$  solution.

In the first group of experiments, 10 to 20 cc. of blood were taken from the basilic vein one-half hour before operation and the same amount from the thyroid veins at time of operation. One cc. of 2 per cent sodium oxalate solution was previously added to the container, the arm and operative field were prepared with picric acid. Patients were in the hospital 16 to 20 hours before operation, consequently the amount of iodine they would absorb by inhalation would necessarily be very small. The diet of the patients was inquired into, and also if they had been employing iodine in any form and when.

Glass stoppered bottles were employed for receiving the blood and not opened until after they were taken from the hospital to avoid any contamination with iodine.

The menstrual history of females was noted, for Veil has shown that during menstruation women have a hyperiodism. This is true also during pregnancy. Of the cases examined, none had iodine in any form for a period of one year previous to hospital admission. However, this is not extremely important, as it has been previously demonstrated that when iodine is ingested orally, blood iodine reached its highest point one and one-half hours after ingestion; nine hours after most of the excess iodine was out of blood stream; twenty-four hours after, the iodine content was just double the normal, and after forty-eight hours it was all eliminated, mainly through the urine.

Eleven cases of ordinary non-toxic goitres were examined with the following results. Controls were done in eight of the cases, with same results, as is shown in Table 1 and Figure 1.

From the results shown in Figure 1 the following observations can be emphasized:

- (1) The thyroid gland must put out approximately as much iodine as it takes in; otherwise in a very short time it would either become overloaded or entirely free of iodine. At most it is thinkable that there are definite periods of storing and releasing of iodine. Our results show that such a regular change, perhaps daily variation, if it happens at all, occurs, at all events, in narrow limits.

TABLE 1

Patient	Peripheral Blood Milligrams Per Cent Iodine			Thyroid Blood Milligrams Per Cent Iodine		
	Colori- metric	Titration	Average	Colori- metric	Titration	Average
A. Z. B. 1883—Female. Duration 10 years. Struma-Nodosa.	10	11.4	10.7	10.0	9.0	9.5
R. T. 1894—Female. Hemi-Thyroidectomy in 1913. Struma-Nodosa.	8.75	9.3	9.03	11.25	11.0	11.13
L. B. 1909—Female. Goitre since Puberty. Struma-Nodosa.	8.75	8.2	8.48	10.0	10.5	10.25
A. G. 1881—Female. Goitre since Puberty. Struma-Nodosa.	11.25	11	11.13	10.0	11.2	10.6
A. N. 1876—Female Goitre 10 years Struma-Nodosa-Cystic.	8.75	9.4	9.08	7.5	8.0	7.75
E. B. 1874—Female Goitre 20 years. Struma-Nodosa	7.50	8.3	7.09	10.25	10.50	10.38
A. T. 1897—Female Goitre 12 years. Struma-Nodosa.	8.75	8.0	8.38	10.0	8.0	9.0
L. M. 1893—Female Goitre since Childhood. Struma-Nodosa.	11.25	11.0	11.13	10.0	11.0	10.5
R. A. 1906—Female. Goitre 6 years Struma-Nodosa.	7.50	7.	7.25	8.75	8.0	8.38
M. G. 1900—Female. Goitre 5 years. Struma-Nodosa.	8.75	8.0	8.36	10.0	10.5	10.25
M. G. 1888—Female Goitre 10 years. Struma-Nodosa.	11.25	11.0	11.13	10.0	12.0	11.0
Average	9.318	9.327	9.322	9.795	9.972	9.883

The fact that in our cases the venous thyroid blood contained as much iodine as that of the general circulation is still of more importance in other ways. It is theoretically possible that part of the iodine taken up by the thyroid gland is again given up to the blood stream by way of the thyroid lymphatic



system. However, this cannot be the case in accordance with our findings. The iodine component of the thyroid secretion, as far as we can conclude from two determinations, has, as a matter of fact, to come directly out of the thyroid gland into the venous blood entirely, or at least in greater part.

(2) In all of the cases, the blood iodine content was somewhat lower than the physiological normal, which would be expected in goitrous individuals. The examinations were also made during the winter season, which accounts for a lower iodine content.

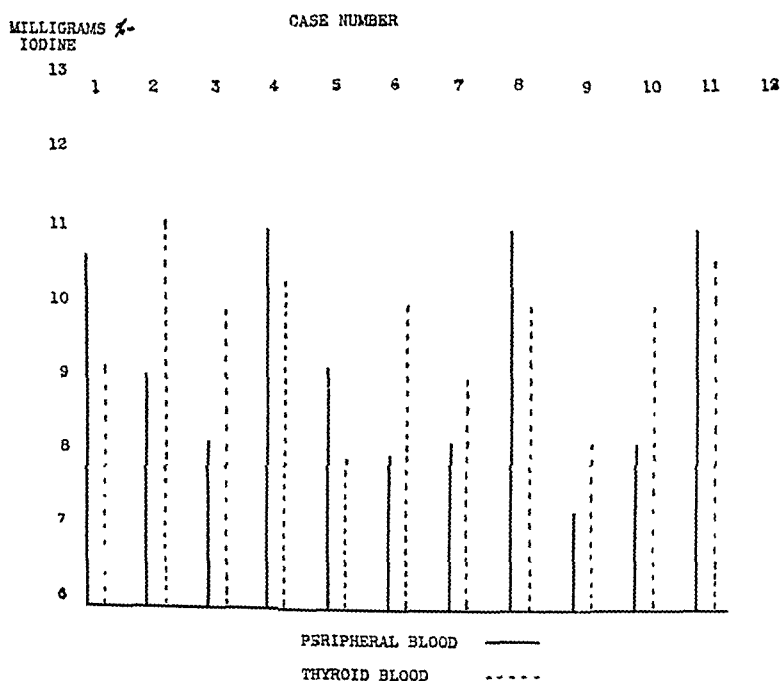


Figure 1. Milligrams per cent iodine in peripheral and thyroid blood.

(3) From these results it can be seen that there is but little variations between peripheral and thyroid blood iodine content. In six cases the iodine content of thyroid blood slightly exceeded that of the peripheral blood. In four cases the peripheral blood showed a slight increase over the thyroid blood. In one case the results were almost identical.

(4) The results seem to indicate:

(a) That the act of iodine intake and output of the thyroid gland occurs without great variations.

(b) That the iodine containing secretion of the thyroid gland arrives entirely, or for the greater part directly into the blood stream and not by the longer route of the lymphatic system.

In further study of the blood iodine problem, the peripheral blood of eleven cretins at Frienisberg, an institution near Bern, was examined, and also the peripheral blood of four normal individuals who were employees at this institution and living under the same conditions, having the same food, etc., as the cretins.

While much has been written on the etiology of cretinism, it is apparently the opinion of most writers that, while thyroid deficiency should predominate in our view of the classic conception of the disease, this is also accompanied by secondary deficiency in the other ductless glands. This is probably due to the lack of iodine in organic combination (thyroidin), for clinical experience has shown that the administering of thyroid gland relieves the symptoms and improves the patient, unless, of course, it is given after irreparable organic changes have taken place.

Knowing that the blood iodine content of cretins is from 50 to 70 per cent lower than normal, we thought it would be of interest to examine the blood of selected cretins and normal individuals at Frienisberg; then to feed or administer the both groups iodine and again examine the blood for its iodine content. After the first determinations were made each individual of both groups was given 0.1 gm. of potassium iodine in table form once daily for a period of seven days.

After a lapse of forty-eight hours to permit normal excretion of iodine, blood was again taken for examination to determine whether or not there was any variation in the iodine content of either group. Tables 2 and 3 show the results.

The striking difference between blood iodine content of cretins and normal individuals is readily seen by glancing at Tables 2 and 3 and Figure 2.

TABLE 2  
CRETINS BEFORE KI ADMINISTRATION

Patient	Colorimetric Milligrams Per Cent Iodine	Titration Milligrams Per Cent Iodine	Average Milligrams Per Cent Iodine
C. K. .... 1884—Male. Typical Cretin, two nodules in struma size of tangerines.	6.25	5.4	5.83
J. M. .... 1882—Male. Twice operated upon—few nodules still present.	7.50	7.0	7.25
E. K. .... 1888—Female. Typical dwarf. Thyroid not palpable.	5.0	5.6	5.3
M. F. .... 1885—Male. Diffuse nodular goitre.	5.0	5.0	5.0
R. H. .... 1871—Female. Cretanoid features—large nodular goitre.	5.0	5.0	5.0
E. S. .... 1896—Male. Type of adult grown cretin, horse- shoe shaped goitre—nodular.	6.25	6.0	6.13
A. G. .... 1881—Female. Typical cretin features.	6.25	7.0	6.63
M. B. .... 1893—Female. Right lobe enlarged, fingers short but not clubbed.	7.50	7.0	6.63
E. A. .... 1890—Female. One large nodule—right.	6.25	6.00	6.13
C. A. .... 1880—Male. One large nodule in isthmus.	5.0	4.0	4.50
A. O. .... 1860—Male. Thyroid not palpable, features monkey-like.	7.50	7.60	7.55
Average. ....	6.70	6.05	6.38

After administering 0.1 gm. of KI for a period of one week, blood was again taken from the both groups and examined with the results shown in Tables 4 and 5 and Figure 3.

By comparing these charts and figures with those just preceding, that is, before KI was administered, it demonstrates that the blood iodine content of cretins remains practically unchanged, while that of normal individuals is increased somewhat.

TABLE 3

NORMALS WITH NO CLINICAL EVIDENCE OF GOITRE BEFORE  
IODINE ADMINISTRATION

Patient	Colorimetric Milligrams Per Cent Iodine	Titration Milligrams Per Cent Iodine	Average Milligrams Per Cent Iodine
H. W..... 1886—Male. At institution 2 years.	12.50	13.65	13.08
H. B..... 1880—Male. At institution 4 years.	13.12	14.25	13.68
G. L..... 1888—Male. At institution 2 years.	11.25	11.0	11.13
L. S..... 1889—Female.	13.75	12.48	13.11
L. E..... 1894—Female.	14.38	14.76	14.57
Average.....	13.0	13.23	13.12

TABLE 4

CRETINS AFTER KI ADMINISTRATION

Patient	Colorimetric Milligrams Per Cent Iodine	Titration Milligrams Per Cent Iodine	Average Milligrams Per Cent Iodine
C. K..... 1884—Male.	6.25	6.5	6.38
J. M..... 1882—Male.	6.75	7.4	7.08
E. K..... 1888—Male.	6.25	6.6	6.43
M. F..... 1885—Female.	5.0	6.2	5.6
R. H..... 1871—Female.	5.6	5.14	5.37
E. S..... 1896—Male.	7.50	7.4	7.45
A. G..... 1881—Female.	7.0	6.5	6.75
M. B..... 1893—Female.	6.25	6.4	6.33
E. A..... 1890—Female.	6.3	6.5	6.4
C. A..... 1880—Male.	5.6	6.0	5.8
A. O..... 1860—Male.	6.9	6.6	6.75
Average.....	6.36	6.48	6.42

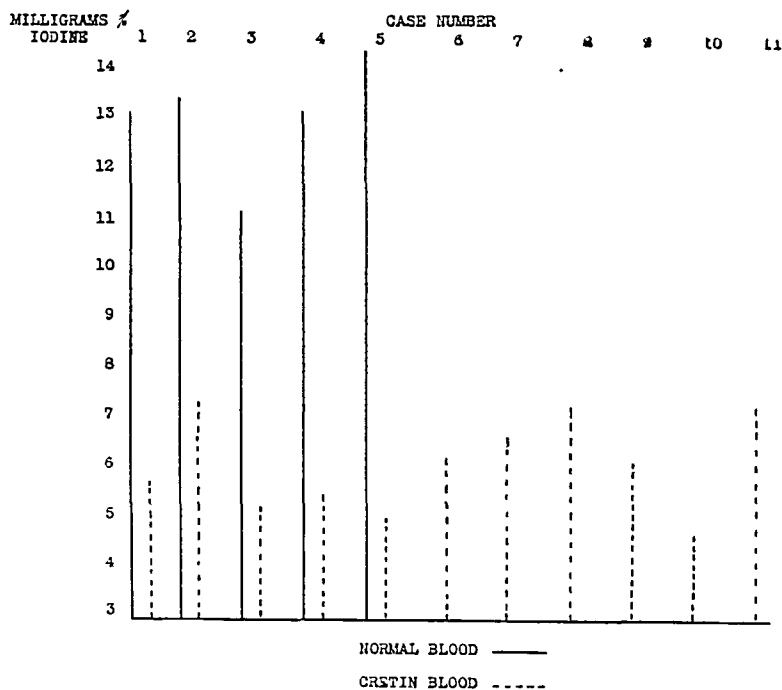


Figure 2. Milligrams per cent iodine in normal and cretin blood

TABLE 5  
NORMALS AFTER KI ADMINISTRATION

Patient	Colorimetric Milligrams Per Cent Iodine	Titration Milligrams Per Cent Iodine	Average Milligrams Per Cent Iodine
H. W. . 1886—Male.	16 25	17 4	16 83
H. B. . 1880—Male.	15 4	14 2	14 35
G. L. 1888—Male.	15 62	16 0	15 81
L. S. 1889—Female.	14 6	14 5	14 55
L. E. 1889—Male.	15 0	15 5	15 25
Average	15 19	15 52	15 36

## CONCLUSIONS

1. The blood iodine content of cretins is persistently fifty to seventy per cent lower than that of normal individuals when on an average diet.

2. The blood iodine content of cretins is practically unchanged by the administration of iodine in the form of potassium iodide, taking blood forty-eight hours after stopping the potassium iodide to allow for normal excretion.

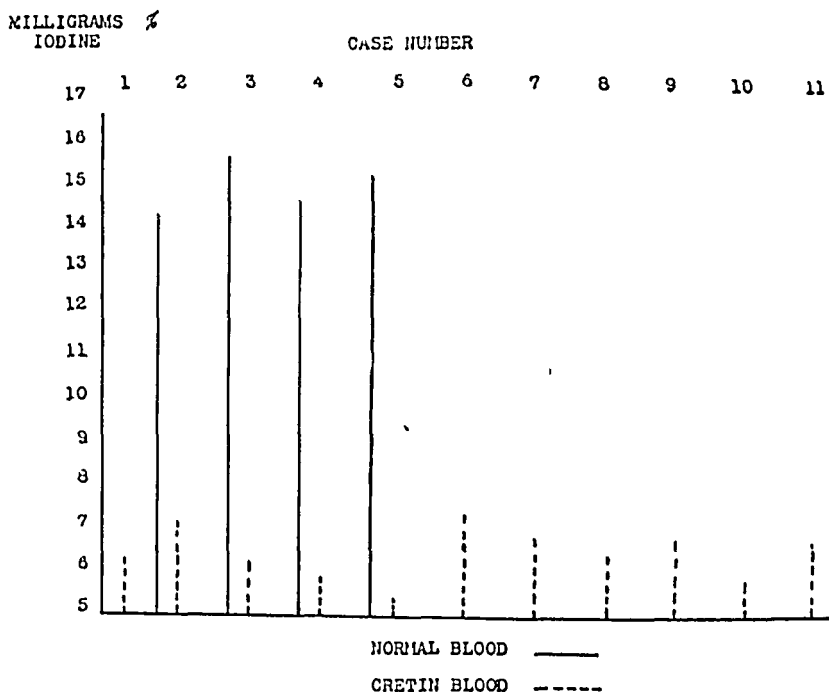


Figure 3. Milligrams per cent iodine in normal and cretin blood after KI administration.

3. The iodine content of a normal individual's blood is somewhat and undoubtedly only temporarily increased after the administration of potassium iodide, allowing the same amount of time for normal excretion.

4. This apparently shows that the cretin retains practically none of the administered iodine, while the normal individual increases his blood iodine content a small amount, but probably only for a short period of time. If the blood had been taken seventy-two or ninety-six hours after ceasing administration, it most likely would have shown no increase over the normal amount.

5. These findings tend to show that the cretin must excrete iodine at a more rapid rate than the normal individual. His powers for retaining iodine, even for a short period of time, are practically nil.

6. According to Veil and Sturm in comparing the iodine content of the Basedow patient, the normal individual, the ordinary goitre patient and that of the cretin, and in accordance with our determinations, we may say that the level of the iodine content is regulated by the organism automatically, according to the degree of function of the gland. In our determinations this regulation would be rather disturbed only for a short period of time by artificial administration of iodine. Thus exists the same self regulation of blood iodine, as the other indispensable elements of metabolism.

With these facts in hand it was desired to determine more conclusively that iodine is excreted by cretins at a more rapid rate than normal. We had a congenial and more or less co-operating cretin who resided at the clinic for demonstrating purposes as being a typical example. Notwithstanding his intellectual deficiency he was quite clever in that each time we desired to withdraw blood from his arm he demanded a package of cigarettes, and promises of tomorrow he would not listen to.

We took this cretin and selected another patient in the same ward who was being treated for a varicose ulcer of the lower extremity. The cretin was admitted to the hospital on October 15th, 1924, and the patient with the varicose ulcer on June 24th, 1926. Both patients received the same amount of potassium iodide and twenty-four hour urine specimens were examined for iodine content.

Dealing with a larger quantity of iodine, Dr. Fellenberg thought it best to modify his original method of determination, and the approximate alterations were as follows:

To 5 cc. of urine was added 2.5 cc.  $K_2CO_3$  solution and sufficient aqua distillata to make 50 cc. One cubic centimeter of this solution equalled 0.1 cc. of urine, which was put into a platinum container and heated on the water bath until vaporized. This was then heated over a flame until the residue was white. After cooling, the residue was dissolved in about 1 cc. of distilled water and placed in an Erlenmeyer flask. The residue was extracted with distilled water three or four times to insure that all the iodine was in solution. One drop of methyl orange was added as an indicator and the solution acidified with dilute hydrochloric acid, adding three drops more of hydrochloric acid to insure acidity. One cubic centimeter of bromine

solution was then added and the solution boiled down to approximately 5 cc. Then we proceeded to determination by titration, as previously referred to.

The results of the comparison of iodine excretion in the urine of a cretin and normal control is shown in Table 6.

TABLE 6

J. G.—1872 Cretin. Admitted to hospital 10-15-24.				E. G.—1884 Varicose Ulcer. Admitted to hospital 6-24-26.			
Date	Amount of KI Admin- istered	24-Hr. Urine	Grms. of KI Excreted	Date	Amount of KI Admin- istered	24-Hr. Urine	Grms. of KI Excreted
6-30-26	0.25	1400 c. c.	0.12	6-30-26	0.25	2400 c. c.	0.08
7- 1-26	0.5	1450 c. c.	0.34	7- 1-26	0.5	1640 c. c.	0.21
7- 2-26	1.0	1830 c. c.	0.68	7- 2-26	1.0	2000 c. c.	0.43
7- 9-26	0.25	1600 c. c.	0.09	7- 9-26	0.25	2100 c. c.	0.09
7-10-26	0.5	1750 c. c.	0.37	7-10-26	0.5	1810 c. c.	0.26
7-11-26	1.0	1920 c. c.	0.52	7-11-26	1.0	2200 c. c.	0.48

On July 2nd, 1926, 20 cc. of blood was taken from the median basilic vein of each patient, before the administration of the morning dose of KI on the 3rd day. This was titrated. The blood iodine content of J. G., the cretin, was 20.52 milligrams per cent, while that of E. G., the normal, was 32.46 milligrams per cent.

#### CONCLUSIONS

The result of this experiment tends to show that cretins excrete iodine through the urine at a slightly more rapid speed than normal. In the six determinations, each of which was repeated three times to insure accuracy of results, the cretin excreted more iodine than the control subject; on the same given amount, in only one determination, the amount excreted was the same.

The blood determination, taken during the course of the experiment, again shows the interesting fact that during the same amount of iodine administration, the blood iodine content of a normal individual is appreciably higher than that of the cretin.

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# GRAVES' DISEASE REDEFINED

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PHILADELPHIA

Since neither exophthalmos nor goiter need be present in otherwise typical instances of Graves' disease, the term exophthalmic goiter as a synonym is confusing and a hindrance to progress in diagnosis and treatment. In my series of 3,343 cases recently reported (1) there was no tangible thyroid enlargement in approximately 20 per cent, and in 15 per cent no exophthalmos existed. In 9 per cent neither exophthalmos nor goiter was observed. The percentage thus atypical would be found considerably greater were it possible to include the many cases in general practice that are undiagnosed because of the absence of both exophthalmos and goiter.

Some time ago (2) I suggested that were Graves' disease removed from the classification of goiter and placed in the category of constitutional affections, the thyroid gland would cease to be incriminated as the etiological factor. The removal of the burden of causation from the thyroid is a procedure with which most investigators are in accord.\* It would also assist in keeping the busy practitioner's mind more alert for the recognition of atypical forms of the disease and would result in a reduction in the number of cases misdiagnosed or recognized only after considerable damage to circulatory and other vital structures has occurred.

Those who see many sufferers from Graves' disease observe that thyroid swelling does not precede but follows such significant signs and symptoms as tremulousness, changes in behavior and emotionalism, undue moisture of the skin, a feeling of unusual warmth, palpitation and dyspnea, fatigability, loss in weight, and an unaccountable tendency toward the speeding up of all physical and mental functions. Swelling of the thyroid, if it occurs at all, is a later event in the evolution of this affection. This would seem to justify the view that the swelling is a

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\* The use of such terms as hyperthyroidism, thyrotoxicosis and toxic goitre, implying thyroid causation of the syndrome, are likewise misleading as synonyms of Graves' disease.

defensive reaction against causative toxins originating elsewhere in the body.

In carefully taken family histories of these patients one is struck with the probability that the disease is the culmination, usually through a psychic trauma as the exciting cause, of a life-long, frequently congenital predisposition to the malady. Commonly there is elicited the information that one or more members of the family are or have been afflicted with nervousness, diabetes mellitus, Graves' disease, or some other condition of nervous or endocrine causation. In the previous medical and personal history goiter is almost never stressed by the sufferer; it is the nervous factors that are brought fully to the fore and complained of as having existed over a period of years.

Prolonged observation of these individuals impresses one with the constancy of three clinical facts:

1. Graves' disease in its active stage\* invariably presents an abnormally high basal metabolic rate. Hence we might safely conclude that whatever its etiology the disease is a *catabolic* disturbance.

2. Almost never does a patient with Graves' disease fail to present marked disturbances of the central and peripheral nervous systems. There is a universal speeding up of nerve function; the threshold of emotional reaction is shortened so that unusual behavior of the patient, asserting itself especially in excitability, is one of the earliest symptoms noted. Autonomic imbalance is evidenced by flushing of the skin, dermatographia, sweating, and the many signs associated now with sympatheticotonia, now vagotonia, again a combination of the two with one or the other predominating. Hence we are also justified in concluding that the disease is largely to be regarded as one of *nervous dysfunction*.

3. The endocrine aspect of Graves' disease is of decided interest. Irrespective of whether the thyroid gland is disturbed qualitatively, quantitatively, or both, it is fairly well established that the disease is not *due* to hyperthyroidism. The majority of observers believe dysthyroidism to be a constituent of Graves' disease, since the *nature* of the thyroid hormone appears to be abnormal. Parathyroid hyposecretion appears probable because of the tremor and low blood calcium content characterizing the

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\* During a marked remission of the disease there may be no abnormal metabolic rate. In this paper we are discussing Graves' disease in its *active* stages.

disease. The commonly observed thymus hyperplasia justifies the belief that this organ is usually in a state of hypersecretion. The lowered carbohydrate tolerance is evidence of hypofunction of the internal secretion of the pancreas. Again, gonadal insufficiency is indicated by the commonly observed amenorrhea and other menstrual disturbances, and sterility. Less certainly, but nevertheless with reason, we might state the suprarenal medulla to be in a state of hyperfunction and the cortex in hypofunction; also that the posterior pituitary is in a state of hypofunction, while the anterior portion of this gland is in hyperfunction. Hence to infer that Graves' disease is an affection of *endocrine dysfunction* appears reasonable.

From the above paragraphs we might state that whatever the cause of Graves' disease, it asserts itself clinically as a *catabolic neuro-endocrine dysfunction*. It would thus appear that we are in position to redefine this affection as follows:

*Graves' disease is a chronic, rarely acute, neuro-endocrine dysfunction characterized by an increased basal metabolism, loss in weight, tremor, emotionalism, persistent afebrile heart hurry, weakness, dermatographia, and usually (not constantly) by hyperplasia of the thyroid gland and by exophthalmos.*

#### CONCLUSIONS

The presence of neither exophthalmos nor goiter is imperative for the recognition of Graves' disease, hence the synonym "exophthalmic goiter" is confusing in the diagnosis of this affection.

The adoption of the above definition of Graves' disease is urged with the hope that it would assist in the elucidation of the nature of this perplexing clinical entity.

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# OBSERVATIONS ON THE ORAL ADMINISTRATION OF THE ŒSTRUS PRODUCING AUTACOID

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It is established that the œstrus producing autacoid, if given in adequate dosage subcutaneously, intramuscularly, intravenously or intraperitoneally, will produce the phenomena characteristic of œstrus in oöphorectomized animals. Hitherto observers have been of the opinion that this autacoid is inactive when taken by the mouth. This view the writer was not inclined to accept until relatively large doses of the autacoid had been exhibited orally in laboratory animals. It was therefore decided to administer the autacoid in large doses to oöphorectomized albino rats with the object of producing, if possible, the vaginal smear changes characteristic of œstrus.

## EXPERIMENTAL CONSIDERATIONS

Virgin female albino rats weighing between 90 and 150 grams each were chosen for the experimental work. It has been shown that rats may, in some instances, remain in anœstrus for weeks at a time, even where the ovaries have been untouched. In order to exclude this type of rat from the series under observation, a dose of 25 rat units of a known active preparation of the autacoid was given subcutaneously in each instance before oöphorectomy was performed, and the capacity for going into œstrus observed. In none of the rats used for this investigation, however, did failure to go into œstrus occur.

With regard to the technique used in the oöphorectomization of this series of rats, some consideration was given to this matter, since it has been observed that œstrus cycles have recurred in some apparently oöphorectomized rats some weeks following operation; post-mortem examination, however, invariably yielding evidence that fragments of the ovaries had been left behind.

It has been suggested that seven to ten days should elapse after oöphorectomy before the animals are used for testing purposes, during which time vaginal smears should be examined daily. It will be obvious that this period would have to be much prolonged to exclude all possibility of any ovarian tissue being left behind. Apart from the fatigue which such a procedure would entail, I have found that some of my animals became insensitive to adequate injections of the autacoid some four weeks following oöphorectomization, possibly due to atrophic changes taking place in the vagina. In one rat atrophy was so marked five weeks after oöphorectomy had been performed that I was unable to insert a medium sized probe into the vagina.

Bearing the foregoing points in mind, it was felt that the only adequate way of making certain that the ovaries had been completely removed was to freely lay open the abdomen and take special precautions to remove all ovarian tissue.

#### OPERATIVE TECHNIQUE

The rats were anæsthetized with ether and, taking all aseptic and antiseptic precautions, the abdomen was freely laid open by a long mid-line incision.

The intestines were turned out and the uterine horns clearly exposed in their whole length, from the vaginal vault to the ovaries on each side. Having identified the ovaries, these were removed, having first clamped the broad ligament and uterine horn for half an inch distal to the ovary. No ligatures were required or applied.

It was possible, in this way, to get an exposure of the ovaries equal to that obtainable in a post-mortem examination. In spite of the severity of the procedure, I had no operative mortality and the rats appeared to be quite well the day following operation.

The oöphorectomized rats were divided into groups of six and allowed to remain for between seven and ten days before being used for testing purposes.

#### ADMINISTRATION OF THE ACTIVE PRINCIPLE

It has been clearly demonstrated that the œstrus producing material can be readily obtained from whole ovaries, and it was decided to feed the rats on these.

*Sows' Ovaries. (Experiment I.)*

The ovaries used were seen to contain numerous active follicles and were therefore presumed to be obtained from animals in full sexual activity.

Day.....	1	2	3	4	5	6	7	8	9	10
No. of rats in oestrus.....	---	---	0	0	0	0	0	---	---	0

---	No observation.
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Twelve of these ovaries were given to 6 rats in one cage. The ovaries proved appetizing and were disposed of within 24 hours. Daily vaginal smears were taken and a search made for the cell changes characteristic of œstrus.

At the end of the 7th day of administration of the ovaries no rats were found to have shown œstral changes during this period. Final smears were taken on the 10th day with negative results.

*Sows' Ovaries. (Experiment II.)*

Day.....	1	2	3	4	5	6	7	8	9	10
No. of rats in oestrus.....	---	---	0	2	2	1	0	---	---	0

In the second experiment, using a new batch of oöphorectomized rats, 3 sows' ovaries were coarsely chopped up and given daily for 4 days.

Care was taken to mop up the follicular fluid, which escaped in the chopping-up process, with bread, this bread being given to the rats in addition to the ovaries.

Daily smears were taken from the vagina as in Experiment I.

On the 4th day 2 rats were found to be in œstrus.

Daily examinations were made for a further 3 days and a final one on the 10th day of this experiment; no more rats, however, went into œstrus.

This experiment seemed promising, hence it was decided to place 6 rats in separate cages and to feed them daily on the maximum quantity of ovarian tissue which they could consume until they all showed the phenomena of œstrus.

*Horses' Ovaries. (Experiment III.)*

It was decided to use horses' ovaries for this experiment as they are very much larger than those taken from sows.

The ovaries chosen for administration appeared to be rich in follicles.

Day.....	1	2	3	4	5	6	7	8	9	10
No. of rats in oestrus.....	---	---	0	1	4	4	6	---	---	---

The amount of ovary consumed per rat was not weighed, but *roughly consisted of one-third to one-half an ovary daily.*

With this method of feeding one rat was found to be in œstrus on the 4th day, 4 rats on the 5th day, 6 rats on the 7th day of feeding. The feeding was then discontinued.

As a further check in this series the rats were killed and a search made for ovarian tissue with, however, negative results.

#### QUANTITATIVE EXPERIMENTS

Having demonstrated that ovarian feeding could be successful in the production of œstrus it was felt that some quantitative work would prove useful.

The product used in this work was the experimental substance "Estrogen" placed at my disposal by Messrs. Parke, Davis & Co.

This product, which is obtained from the placenta, is issued as containing 25 rat units per cc., as assayed by the formula:

$$\text{Rat Units per cc.} = \frac{W}{140 Q}$$

W represents the weight of the rat in grams.

Q represents the minimum number of cubic centimetres of the preparation which causes typical œstrus in any rat used in the test.

Samples were taken from the batches of ampoules which were supplied for this work and tested for activity. One batch proved totally inactive, but in the remainder the activity was found to be as indicated. The apparent irregularity in the activity of this particular product has occurred in specimens of the œstrus producing autacoid prepared by myself on a small scale and, furthermore, has been found to occur in all samples of commercial products which I have tested.

I have found the substance tested to be either totally inactive or active to the extent anticipated or indicated; this fact points, I think, to the œstrus producing autacoid, being somewhat unstable in nature.

Incidentally, the work of Bugbee and Simond (1926), in which they report experiments which demonstrate that the dose of the œstrous producing autacoid should vary according to the body weight of the rat, was confirmed.

Furthermore, opportunity was taken of controlling the specificity of this substance by giving control injections of acetone and alcohol extracts of brain and testicular tissue. No œstrus was produced by either of these substances.



*Estrogen Feeding. (Experiment IV.)*

Day.....	1	2	3	4	5	6	7	8	9	10
No. of rats in oestrus.....	---	0	5	6	---	---	---	---	---	---

Five hundred rat units were dissolved in the animals' drinking water which was common to all 6 rats under observation.

Oestrus changes were detected in 5 rats on the 3rd day of the experiment and 6 rats on the 4th day.

*Estrogen Feeding. (Experiment V.)*

Day.....	1	2	3	4	5	6	7	8	9	10
No. of rats in oestrus.....	---	0	1	2	0	0	---	---	---	---

Three hundred rat units were administered in a similar way to that used in experiment IV and utilizing the same rats. An interval of 7 days elapsed between this and the previous experiment.

Three rats only in this group went into oestrus, one on the third day and 2 on the fourth day of the experiment.

*Estrogen Feeding. (Experiment VI.)*

Day.....	1	2	3	4	5	6	7	8	9	10
No. of rats in oestrus.....	---	0	0	0	0	0	---	---	---	---

One hundred fifty rat units were administered in a similar way to that adopted in Experiments IV and V.

The results in this series were entirely negative over a period of 5 days' observation.

## DISCUSSION

In experiments IV, V and VI between 300 and 500 rat units proved necessary to produce oestrus in 6 observed rats when the product was administered by the mouth.

The combined weight of the rats used in these experiments amounted to 909 grams, giving an average weight of 151.5 grams per rat.

Taking the mean of the figure 300 and 500, *i. e.*, 400, as being the number of rat units necessary to produce oestrus in 6 rats of

an average weight of 151.5 grams each, we obtain the figure of 66.6 as being the number of rat units necessary to produce oestrus in a rat of 151.5 grams, the product being administered orally.

Utilizing the formula of standardization which I have mentioned previously, the amount which should prove necessary to produce oestrus in a rat of 151.5 grams would be 1.08 rat units. Oral administration, however, required 66.6 rat units.

It would appear therefore that the ratio of activity of the oral method of administration to the subcutaneous is 1:61.6.

#### SUMMARY

(1) The oestrus producing autacoid is active if administered by the oral route in adequate dosage.

(2) The dose required is some sixty times larger than that which is necessary when the hormone is administered by injection.

I am particularly indebted to Professor Swale Vincent for providing me with laboratory facilities in connection with this work, also for much help and constructive criticism in the conduct of the experimental work.

I also wish to acknowledge the courtesy of Messrs. Parke, Davis & Co., in providing me with adequate supplies of their experimental product, Estrogen, used in this investigation.

The expenses of the investigation were in part defrayed by a grant\* to Professor Swale Vincent, which he kindly diverted to this purpose.

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\* From the British Association (Ductless Glands Committee).

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# THE EFFECT OF DUODENAL SECRETIN UPON THE SECRETION OF INSULIN BY THE PANCREAS

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In a previous work (Nóvoa Santos, Criado and Barreiro, 1924), it was shown that intravenous injections of duodenal secretin into both men and lower animals produced in all cases a marked hypoglycemia. Independently of our work, Penau and Simonnet (1925) came to the same conclusions. Criado, working in my laboratory has later confirmed these results, the data of which will soon be published in detail. Some of the results obtained are given in the accompanying tables.

A comparative study of the action of insulin and secretin upon blood sugar shows that the effect of insulin is the more intense. The following data show this effect:

## BLOOD SUGAR IN DOGS INJECTED WITH 1 CC. OF SECRETIN

	Before Injection	15 Minutes After Injection	30 Minutes After Injection	1 Hour After Injection
I.	1.15 per 1,000	1.5	1.15	1.00
II.	1.15 per 1,000	1.00	0.92	0.92
III.	1.32 per 1,000	0.82	0.80	0.60
IV.	1.39 per 1,000	1.17	1.17	1.06
V.	1.35 per 1,000	1.39	1.60	...
VI.	1.18 per 1,000	1.50	1.03	1.50

## RABBITS INJECTED WITH 1 CC. OF SECRETIN

	Before Injection	15 Minutes After Injection	30 Minutes After Injection	1 Hour After Injection
I.	1.00 per 1,000	0.85	0.95	0.95
II.	1.20 per 1,000	1.02	0.90	0.90
III.	1.86 per 1,000	1.00	0.95	1.05
IV.	1.17 per 1,000	1.09	1.03	1.10
V.	1.23 per 1,000	1.10	1.02	1.05
VI.	1.64 per 1,000	1.64	1.70	1.21

## MEN INJECTED INTRAVENOUSLY WITH 1 CC. OF SECRETIN

	Before Injection	15 Minutes After Injection	30 Minutes After Injection	1 Hour After Injection
I.	1.25 per 1,000	1.21	1.14	0.80
II.	1.14 per 1,000	1.14	1.39	0.89
III.	1.07 per 1,000	0.96	0.64	0.75
IV.	1.28 per 1,000	1.21	0.80	1.28
V.	1.00 per 1,000	0.89	0.82	0.75
VI.	1.10 per 1,000	0.53	0.71	0.71

RABBITS INJECTED WITH 1 CC. OF SECRETIN AND 10 UNITS  
OF INSULIN

SECRETIN				
	Before Injection	15 Minutes After Injection	30 Minutes After Injection	1 Hour After Injection
I.	1.20 per 1,000	1.02	0.90	0.90
II.	1.17 per 1,000	1.09	1.03	1.10
INSULIN				
I.	1.25 per 1,000	1.00	0.86	0.64
II.	1.20 per 1,000	0.64	0.60	0.64

## DOGS INJECTED WITH 1 CC. OF SECRETIN AND 10 UNITS OF INSULIN

SECRETIN				
	Before Injection	15 Minutes After Injection	30 Minutes After Injection	1 Hour After Injection
I.	1.15 per 1,000	1.15	1.15	1.00
II.	1.32 per 1,000	0.88	0.80	0.60
INSULIN				
I.	1.03 per 1,000	0.58	0.82	0.90
II.	1.42 per 1,000	0.50	0.30	0.30

In our previous work we advanced the hypothesis that this hypoglycemic action of secretin was perhaps due to its contain-

ing some active substance, such as the internal secretion of the pancreas. We have, however, no data that would confirm such a supposition. Penau and Simonnet do not think that the hypoglycemic reaction is caused by the internal secretion of the pancreas, since in the depancreatized dog this hypoglycemic action of secretin is still obtained, as in the normal animal. Lambert and Hermann (1925) also have reported that the variations in blood sugar caused by secretin persist after the extirpation of the pancreas. In two pancreatectomized dogs we have been unable to find any significant variations in blood sugar following the injection of secretin. In one of these animals the fasting blood sugar was 2.78 per 1000. Fifteen minutes after the injection of 1 cc. of secretin the blood sugar was 3.25. Half an hour after the injection the blood sugar was 3.03; an hour after the injection, 3.03. In the second animal the fasting blood sugar level was 3.45 per 1000. After the injection of 2 cc. of secretin, in fifteen minutes the blood sugar was 3.45; in half an hour, 3.64; in an hour, 3.57. Other experiments gave similarly negative results.

In spite of these results, it is not believed that the problem is yet definitely settled. These data are given in view of the work reported by Freud and Saddi-Nazim (1926) in which they agree with a point of view expressed by me that duodenal secretin has an activating influence upon the pancreatic islands. Freud and Saddi-Nazim have shown that in a half hour after the introduction into the duodenum of 50 to 100 cc. of 5 per cent HCl, the blood sugar content is diminished. This condition persists for an hour, and may be obtained even after the destruction of the digestive acinar portion of the pancreas by ligation of the duct. The conclusions reached by these workers and by Gley (1926) are that the duodenal secretin produced by the introduction of HCl into the duodenum, stimulates the production of insulin, but that the hypoglycemia is due to the secretin produced and not to the insulin. Hence, their interpretations agree with the results of the experiments of Simonnet, Lambert and Hermann and with our colleagues.

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# A SEX DIFFERENCE IN INTESTINAL LENGTH AND ITS RELATION TO PITUITARY SIZE

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Clinical observations have indicated that hypersecretion of the anterior lobe of the pituitary gland is associated with splanchnomegaly. Cunningham, according to Barker (1), reported a case in which the length of the small intestine was doubled. In the human, however, we are quite without data concerning intestinal length in the normal male and female; and, apparently, the weight of the pituitary is available for only four normal men and one woman (2). Here the female pituitary was larger, in the ratio 1.5:1.

In rats the pituitary of the female is definitely known to be larger than that of the male. For Albino, the data of Hatai (3) and of Jackson (4) show values of 8.9 and 15.8 mgms. in males and females, respectively. Addison and Adams (5) have further shown that though the female *pars nervosa* is somewhat larger, the female *pars anterior* is more than double that of the male. From the wild Norway rat Hatai (6) obtained data from 31 males and 17 females. The body weight of the males was somewhat greater (males, 252 grams; females, 227 grams), but in them the hypophysis averaged smaller (8.0:8.4 mgm.). On the other side of the present problem—that of intestinal length—no measurements are available for the rat.

The data of this communication make it entirely clear that female Ring doves have longer intestines than the males. And in this family of animals some data on pituitary size are at hand. McCarrison (7) has earlier concluded that "in healthy common pigeons the pituitary is considerably heavier in the females than in the males." Altogether, McCarrison weighed 69 pituitaries. In healthy males and females he got averages of 5.3 and 5.9 mgms. (19.3 and 22.1 mgms. per kgm. body weight); from birds with dietary deficiency he obtained nearly similar values (5.8 and 6.3 mgms.; or, 19.6 and 22.4 mgm. per

kgm. body weight). These data are probably insufficient for a valid determination of this point; we can now, however, add a few weighings on pituitaries of similar common pigeons which tend to confirm this sex difference in pituitary size. It thus results that the doves and pigeons provide us with data definitely showing that the females have longer intestines (doves), and that this is probably associated with larger pituitaries (pigeons).

TABLE 1

Length of Intestine in Five Racial Groups of Ring Doves and Ring Hybrids

Race or Group	Healthy or with Ascaridia	No.	Body Weight Grams	Average Intestinal Length Centimeters	Seasonal Mean	Per Cent* Excess in Females
MALES						
Ring A.....	Healthy ...	78	152	49.75	49.9	
	Ascaridia ..	78	158	50.7	50.45	
Ring B.....	Healthy ...	49	156	55.55	55.95	
	Ascaridia ..	20	151	57.05	57.35	
Ring C.....	Healthy ...	26	166	50.5	49.6	
	Ascaridia ..	15	169	52.4	52.1	
Group 4.....	Healthy ...	171	159	52.6	52.4	
	Ascaridia ..	59		54.6	54.8	
Trispecific ...	Healthy ...	53	162	49.6	49.6	
	Ascaridia ..	27		52.6	53.9	
FEMALES						
Ring A.....	Healthy ...	70	150	51.35	50.45	3.2
	Ascaridia ..	76	150½	52.75	53.25	4.0
Ring B.....	Healthy ...	32	149	57.4	57.45	3.3
	Ascaridia ..	21	152½	60.85	61.45	6.7
Ring C.....	Healthy ...	13	164	53.9	54.4	13.0
	Ascaridia ..	13	162	60.0	58.9	14.6
Group 4.....	Healthy ...	157	155	54.6	55.4	3.9
	Ascaridia ..	121		58.1	57.5	6.8
Trispecific ...	Healthy ...	38	154	53.9	54.1	8.7
	Ascaridia ..	40		56.9	54.9	8.2

In Table 1 the intestinal length is given for males and females of five "groups" of ring dove (*Streptopelia*) races. The races of "Group 4" contain traces of another genus. The "trispecifics" are contaminated with *St. douraca*. Birds with

\*The average for each race was first obtained (12 races in "group 4"); an average for the group, as listed, then found.



disease other than ascariasis are entirely omitted; birds bearing *Ascaridia* are classified apart from the healthy animals. Five racial groups are listed. In obtaining the figures tabulated the two or more races which form each racial group were separately tabulated, and indeed on the basis of season—since the possibility of seasonal change exists. Both the average and the seasonal mean for intestinal length was calculated. Each race within the group—though represented by unequal numbers of individuals measured—was made coequal with the others in deriving the figures as tabulated. The measurement is for that part of the intestinal tract lying between the gizzard and the anus. The birds were killed by decapitation. Shortly after all intestinal movement had ceased, the abdominal cavity was opened; the intestine was then removed; the mesenteric folds enforcing all curvatures were torn apart; and finally, the intestine laid (with as nearly uniform stretching as possible) on a horizontal meter-stick for measurement. It is important to note that all these data are from sexually mature animals (6-30 months).

In all of the 10 comparisons afforded by the table the female intestine exceeds that of the male in length. This also despite the fact that the body weight of the males exceeds the weight of the females by about 2 per cent. It is further shown that ascariasis is associated with increased length of intestine in both sexes. The data were obtained from 377 healthy, and 199 ascariasis males; and from 310 healthy, and 271 ascariasis females. These data from 1157 birds leave no doubt that a sex difference in intestinal length exists in adult ring doves—the female intestine is both absolutely and relatively the longer. With body weight considered the difference averages 5-10 per cent.

It should here be noted that we have also obtained several hundred measurements of intestinal length in various races of common pigeons. On account of wide racial differences there these must, however, be treated as several different groups. A still greater source of trouble is found in the fact that in these pigeons an unrecognized disease—marked in its later stages by great emaciation and extreme intestinal length—is at times rather prevalent in these forms. Early stages of this disease

or size of the anterior lobe—the latter being a thing very difficult to measure in most laboratory animals.

#### SUMMARY

Adequate data from adult ring doves show that the females of these forms have longer intestines (5-10 per cent) than the males. The presence of *Ascaridia* is here associated with increased length of intestine in both sexes.

Some new data for pituitary size in pigeons of both sexes agree with earlier data (McCarrison) in indicating that in these animals the females have larger pituitary glands.

The few items of adequate data now available for man, rat and bird lead to the conclusion that there is a sex difference in both pituitary size and intestinal length, and that this difference involves a larger pituitary (particularly anterior lobe) and a longer intestine in the female. Some biological and clinical applications of these results are suggested.

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# Abstract Department

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**Influence of the sodium salt of barbital on the effects of adrenin**  
(Action de la diéthylmalonylurée sodique sur les effets vasculaires de l'adrenaline). Arnell, O., *Compt. rend. Soc. de biol.* **97**: 1633-1635. 1927.

When tested on a frog, sodium barbital in dilute solution, 25 parts in ten million, markedly reinforced the effects of dilute adrenin as shown by the slowing of the heart.—J. C. D.

**Modification of adrenalin effect with functional status of stomach.**  
Arquin, S. F. *Proc. Soc. Exper. Biol. & Med.* **25**: 97-99. 1927.

The work was done on normal trained dogs. Stomach balloons were passed by mouth, and records taken on a kymograph. After a suitable control period 10 minims of 1:1000 adrenalin was injected intracutaneously. It was found that the actively digesting stomach showed no reaction to adrenalin; the starving stomach in hunger contraction showed dilatation, with inhibition of contractions, in reaction to adrenalin; the starving stomach in the quiescent state was thrown into forcible hunger contractions. It is concluded that the tissue cells proper, or the myoneural filaments, by their tonus at the time of stimulation, are the determining factors as to the direction of reaction to adrenalin.—Author's Abst.

**The fate of sugar in the animal body. VII. The carbohydrate metabolism of adrenalectomized rats and mice.** Cori, C. F., and Gerty T. Cori, *J. Biol. Chem.* **74**: 473-493. 1927.

When rats surviving double adrenalectomy were subjected to a 24-hour fast, the liver glycogen disappeared and the blood sugar fell considerably below normal. In contrast to the liver glycogen, the glycogen content of the muscles of these animals remained the same as that of normal control rats fasted for the same length of time. The absence of liver glycogen in fasting adrenalectomized rats is not the result of a disturbance in the synthesis of sugar into glycogen, since liver glycogen is formed at a normal rate when glucose is fed. Adrenalectomized rats, fasting 24 hours, absorbed glucose at a much slower rate than 24-hour fasting normal rats. During 4 hours of glucose absorption the adrenalectomized rats without insulin oxidized 373 mgm. of glucose and formed 270 mgm. of glycogen (124 mgm. in the liver and 146 mgm. in the rest of the

body). The adrenalectomized rats receiving insulin injections oxidized 471 mgm. of glucose and deposited 37 mgm. of glycogen in the liver and 185 mgm. of glycogen in the rest of the body. The difference in liver glycogen of 87 mgm. corresponds closely to the difference in glucose oxidation of 98 mgm., while the glycogen deposition in the rest of the body (chiefly muscles) is slightly increased. The same results have been obtained previously on rats with intact adrenals, while a discharge of epinephrin in sufficient amounts to produce a metabolic effect could not be excluded. Since the adrenals were absent in the present experiments, the conclusion has been drawn that the lessened deposition of liver glycogen and the increased sugar oxidation, also to be observed in insulinized rats with intact adrenals, are due to insulin alone and not to a combined action of insulin plus epinephrin. Previous experiments have shown that insulin injections lead to a decrease in liver glycogen of fasting insulinized mice. An identical result has been obtained on mice from which both adrenals had been removed 20 to 30 days previously. The adrenalectomized mice without insulin showed 2.16 per cent liver glycogen after a fasting period of 1 to 5 hours. The adrenalectomized and insulinized mice that were killed simultaneously showed only 0.79 per cent liver glycogen. Since the effect of insulin on the liver glycogen of fasting animals is the same, whether or not the adrenals are present, there is no need to assume that epinephrin is responsible for the decrease in liver glycogen following insulin injections.—Author's Abst.

the depressor (vaso-dilator) action of adrenalin. Dale, H. H., and A. N. Richards, *J. Physiol.* 63: 201-210. 1927.

An investigation was made of the alleged vasodilator effect due to liberation of histamine from the lung following small intravenous injections of adrenalin. The greater effect produced by intravenous injections as compared to intra-arterial injections reported by Burn and Dale (*J. Physiol.*, 61: 185. 1926) was found to be due to a technical error. The authors confirmed the conclusion that the vasodilator effect of adrenalin is due to peripheral action. However, it was observed that an injection of adrenalin into the arterial supply to the brain when the tone of the vasomotor center was raised by restricting the blood supply produced a very powerful depressor effect, apparently due to direct effects on the center.

—C. I. R.

Observations on hemodynamic effect of epinephrine in unanaesthetized dogs. Dragstedt, C. A., and A. H. Wightman, *Proc. Soc. Exper. Biol. & Med.* 25: 22-24. 1927.

Observations following the continued intravenous administration of epinephrine in unanaesthetized dogs and dogs slightly narcotized with morphine are reported. Pressor effects were found to

occur with doses between 0.12 cc. and 0.5 cc. of 1 to 1 million adrenalin per kgm. per minute. Depressor responses were not seen. In animals in which depressor effects were seen during ether anaesthesia, only pressor effects were seen after recovery from the anaesthesia.—C. A. Dragstedt.

**The vasomotor action of adrenin on muscle (Actions vasomotrices de l'adrénaline sur les muscles. Processus périphérique vaso-constricteur et processus central vaso-dilatateur.)** Gayet, R., T. Gayet and M. Guillaumie, *Compt. rend. Soc. de biol.* **97**: 1145-1147. 1927.

The measurements were made on the paws of dogs anaesthetized with chloralose. Paw (I), Dog (A), was normal. Paw (II), Dog (A), was amputated and circulation maintained with Dog A by tubes. Paw (III), Dog (B), was amputated save for the sciatic and crural nerves and circulation derived from Dog A. Paw (IV), Dog (B), was normal. From their experiments with this arrangement, the authors conclude that the influence of adrenin on the circulation of muscle is, excluding the effects of changes in blood pressure in the general circulation, the result of two actions separate and opposed. Regardless of the dose there is constriction of peripheral origin and dilatation having its origin in the central nervous system.

—J. C. D.

**New researches on the heart-hormone (Neue Herzhormonbefunde).** Haberlandt, L., *Klin. Wchnschr.* **44**: 2099. 1927.

The activity of solutions containing the heart stimulating hormone or the hormone in the heart itself are not destroyed by exposure to daylight, light from an incandescent lamp, ultra-violet light and Roentgen ray. Consequently this hormone differs from the cardiac accelerating substance of Loewi and adrenalin, which are destroyed by such treatment.—L. R. Dragstedt.

**Glutathione and the reducing properties of tissues of decapsulated rats (Le glutathion et les propriétés réductrices des tissus des rats décapsulés).** Houssay, B. A., and P. Mazzocco, *Compt. rend. Soc. de biol.* **97**: 417-419. 1927.

The striking result was the increased reducing power of muscle and kidney when tested with glutathione in the decapsulated animals. This reached a maximum at eight to fifteen days after operation and was normal after about thirty days. This reaction does not agree with the results when m-dinitro-benzene is used to test with, but is confirmed by the intensity with which the muscles stain in the nitroprussiate reaction.—J. C. D.

**The vagus nerve and the secretion of adrenin from the adrenals (Nerfs pneumogastriques et sécrétion surrénale d'adrénaline).**

Houssay, B. A., and E. A. Molinelli, *Compt. rend. Soc. de biol.* 97: 1343-1344. 1927.

Dog experiments in which the vagus was cut under local anaesthesia indicate that the vagus has no vasomotor effect either direct or reflex on the secretion of adrenin.—J. C. D.

The oral administration of epinephrine. Menninger, W. C., *Arch. Int. Med.* 40: 701-714. 1927.

The author gives a rather complete review of the literature. He reports observations on 21 patients (16 of whom showed evidences of hyperthyroidism) following the oral administration of 2 to 6 mgm. of epinephrine in gelatin capsules on an empty stomach. A decrease in blood pressure of from 2 to 10 mm. was seen in 9 cases; no change in pressure in 6 cases; increase in pressure of from 5 to 15 mm. in 6 cases, and increase in pressure of 15 mm. or more in 7 cases. The rises in the latter seven were 16, 18, 20, 28, 30, 50, and 110 mm. Hg. The increased blood pressure lasted from 35 to 90 minutes. Abdominal cramps, substernal distress, respiratory distress, nausea, tremor, sweating and vomiting were also seen in some cases. The author concludes that the oral administration of epinephrin is inconstant and unreliable, but that in certain cases it is undoubtedly absorbed from the gastro-intestinal tract.

—C. A. Dragstedt.

The action of adrenin in asthma and hay fever (*Le mécanisme de l'action de l'adrénaline dans l'asthme et le coryza spasmodique*). Peruche, de Paula, *Compt. rend. Soc. de biol.* 97: 1062-1064. 1927.

The author concludes that the efficiency of adrenin in asthma is due to its influence on CO<sub>2</sub>. There is increased CO<sub>2</sub> in the blood in these conditions. Adrenin reduces the CO<sub>2</sub> tension in the blood, increases the CO<sub>2</sub> in exhaled air, reduces the CO<sub>2</sub> alveolar tension, but does not influence the pH of the blood.—J. C. D.

The hypertensive action of adrenalin following various routes of administration (*L'action hypertensive de l'adrénaline suivant la voie d'introduction dans l'organisme*). Plumier-Clermont and L. Garot, *Arch. int. Physiol.* 26: 362-388. 1926.

Experiments are reported in which adrenalin was administered to dogs in various ways and the resultant effect on the blood pressure noted. No mention is made of the anaesthetic used. Subcutaneous injections of dilutions from 1-10,000 to 1-100,000 in doses of 1/60 to 1/3 mgm. per kgm. gave no clear-cut effects on the blood pressure, but quite regularly a slowing of the pulse. There was no relation between the effects observed and the size of the dose. Intramuscular injections of dilutions from 1-1,000 to 1-10,000 in doses of 1/10 to 1/3 mgm. per kgm. gave inconstant results, but there

was a greater tendency to pressor effects than on subcutaneous injections, which they attribute to better absorption. Slow intravenous injections of dilutions of 1-100,000 at a rate of 1 cc. per minute gave no appreciable effect. Larger doses gave pressor effects. No mention is made of any depressor effects. Administration via the gastrointestinal tract was made by laparotomy and injection of the adrenalin into the stomach or bowel by hypodermic needle. Doses of 1/20 to 1/2 mgm. per kgm. gave usually a fall in blood pressure of approximately 10 mm. Injection of adrenalin into the mesenteric vein was much less effective than by peripheral veins. This they attribute to a neutralization or storing in the liver and thus explain the ineffectiveness of gastrointestinal administration. Rectal administration they found more apt to be effective than gastric or intestinal, and attribute this to better absorption on the one hand and escaping the liver on the other. Intra-arterial injection was much less effective than intravenous, and there was a larger latent period. This they relate to the constitution of the arterial wall and the interposition of a capillary bed.—C. A. Dragstedt.

**Does adrenin exert a stimulating action on the vaso-motor centers?**

(L'adrénaline exerce-t-elle une action stimulante sur les centres nerveux vaso-moteurs?). Tournade, A., Compt. rend. Soc. de biol. 97: 1143-1144. 1927.

The kidney of a dog (A) was manipulated so that the blood supply was derived from a second dog (B), but the nerve supply from dog A remained intact. Intravenous adrenin injections into dog A resulted in the kidney dilating, contracting, or one condition following the other. There is an action of adrenin directly on the central nervous system causing vaso-constriction, but this is usually masked by the vaso-dilation, due also to action directly on the central nervous system.—J. C. D.

**The effect of adrenalin on intestinal volume.** White, A. C., J. Pharmacol. Exper. Therap. 32: 135-147. 1927.

In anaesthetized or decerebrated cats, after bilateral vagotomy, intravenous injection of adrenalin in doses varying from 0.0129 mgm. to 0.0323 mgm. per kilogram showed generally a diminution in intestinal volume. With doses varying from 0.0004 to 0.0732 mgm. per kilogram the predominant effect was an increase. In some cases there was a preliminary decrease followed by an increase in volume. Volume changes were independent of blood pressure.

—C. I. R.

**Some recent advances in our knowledge of the ductless glands.** Abel, J. H., Med. Clin. N. A. 11: 113-126. 1927.

The physiological, chemical and pharmacological properties of the various endocrine glands are discussed. The problem as to

whether the posterior lobe of the pituitary body has one or three or more specific principles is discussed, and it is concluded that there is only one active principle. Inherent in this one principle are a surprising number of various physiological properties. Compared with histamine, heretofore the most powerful oxytocic or uterus-contracting agent known to medical science, the best and final posterior-lobe tartrates are found to be from 1,000 to 1,250 times more powerful. Corroborating support of various experimenters that there is only one posterior-lobe principle is quoted. The structure, functions, and chemical principles of the hypophysis cerebri are described to make evident what difficulties are encountered in the study of any one of the organs of internal secretion.—I. B.

**Endocrine disorders as related to more common syndromes.** Hutton, J. H., *Med. Clin. N. A.*, 11: 113-126. 1927.

This paper is a plea that more attention be given the endocrines by the profession at large in general physical examinations. An investigation of the condition of the ductless glands should be just as routine a procedure as the determination of the condition of the circulatory, gastrointestinal or genitourinary systems. Endocrine disorders are more prevalent than is generally supposed, and when discovered during their incipency respond readily to appropriate treatment.—I. B.

**Changes in water content of the liver as influenced by some of the internal secretions** (*Variations de la teneur en eau du foie après quelques modifications de l'équilibre endocrinien*). The effect of insulin, thyroid extract, and adrenin on the water content of the liver. The thyroid-adrenal-pancreatic relationship (*Action de l'insuline, de la thyroïde et de l'adrénaline sur la teneur en eau du foie. Correlations thyro-surréno-pancréatiques*). Parhon, C. I., M. Cahane and V. Marza, *Compt. rend. Soc. de biol.* 97: 1115-1118. 1927.

In sheep, thyroid extract increases the water content of the liver to a marked degree, adrenin less so, while insulin reduces it.

—J. C. D.

**Influence of transplantation on the sex characters of earth-worms** (*Expériences de transplantation sur les caractères sexuels secondaires des lombriciens*). Avel, M., *Compt. rend. Soc. de biol.* 97: 1069-1070. 1927.

Transplantation after puberty does not influence the sexual cycle, but removal of the gonads before puberty prevents the development of the sexual cycle.—J. C. D.

**Changes in the ovary of the mouse following exposure to x-rays.**  
**III. Irradiation of non-parous adult.** Brambell, F. W. R., and A. S. Parkes, *Proc. Roy. Soc.* 101B: 316-328. 1927.



Seventy-five per cent of adult animals killed five weeks or more after radiation were sterilized. The oestrous cycles of these animals were not interrupted. Oocytes of the small follicles were destroyed, leaving persistent "anovular" follicles. The cortical elements of the ovaries persisted and continued to produce oestrin without interruption after irradiation.—E. A.

**Studies on distribution of the follicular hormone in the body (Recherches sur la distribution de la folliculine dans l'organisme).** Brouha, L., and H. Simonnet, *Compt. rend. Soc. de biol.* **97**: 459-460. 1927.

The placenta of the cow and uterine muscle of the cow and mare were examined in addition to human blood from patients in various conditions. The authors conclude in part that in the organs examined the hormone, when found, was in weaker concentration than in the follicle. It, or a similar substance, exists in the blood during gestation. It is not present in the resting uterus. It is found in milk. In certain chronic amenorrheas it is found in the blood.—J. C. D.

**Production of male characteristics in capons and senile cocks by injection of serum from young males. Activation by previous injection into the young males of serum from senile animals (Détermination ou retour des caractères de masculinité, chez les chapons et les vieux coqs, par le sérum de jeunes animaux males. Activation du sérum par injection préalable au jeune male de sérum de vieil animal).** Busquet, H., *Compt. rend. Soc. de biol.* **97**: 1463-1465. 1927.

The author concludes in part: Serum from young bulls, stallions, and rams cause the reappearance of male characters in capons and senile cocks. If a young bull is injected with serum from a senile bull, the serum from the young bull shows a marked increase in effects. The serum shows its full effects when given by mouth.  
—J. C. D.

**Gonad stimulating hormone of anterior pituitary and heterosexual ovarian grafts.** Engle, E. T., *Proc. Soc. Exper. Biol. & Med.* **25**: 83-84. 1927.

Ovaries from 20-day old rats were transplanted into the abdominal muscles of adult castrated rats and into the testis of normal adults. Daily homeo-transplants of the anterior pituitary cause a high degree of follicular development in the ovario-testis. The ovarian graft in the testis does not differ histologically from that in the castrated male. The seminal epithelium of the host is normal in character. Although the elapsed time was short, there is no apparent "antagonism of the sex glands."—Author's Abst.

**Pregnancy following superovulation in the mouse.** Engle, E. T., *Proc. Soc. Exper. Biol. & Med.* 25: 84-85. 1927.

Superovulation may be induced in the mouse and rat by daily transplants of the anterior pituitary, with from 20 to 48 ova in each uterine tube, as reported by Smith and Engle (*Am. J. Anat.*, 40).

Superovulation is followed by pregnancy in the mouse with from 19 to 29 fetuses recovered on the 9th or 10th day of pregnancy.—Author's Abst.

**Clinical data obtained with the female sex hormone blood test.** Frank, R. T., and M. A. Goldberger. *J. Am. M. Ass.* 90: 106-110. 1928.

The ovarian hormone content of the blood of 86 subjects was investigated by mouse estrous assays. It was concluded that in women with normal sex cycle, more and more of the female sex hormone accumulates in the circulating blood until menstruation sets in. With the onset of menstruation, as well as with the beginning of pregnancy, the hormone disappears from the circulating blood. The hormone is found in great concentration in the menstrual as well as in the postpartum blood. The hormone is found in the circulating blood from the twelfth to the fortieth week of gestation. In functional bleeding a majority of cases show excessive ovarian activity. Functional overactivity may be demonstrated without excess bleeding ("tension"), and even in the presence of amenorrhea. Amenorrheas must be subdivided into (a) a grave type without cycle, and into those with (b) subthreshold cycle, (c) self-limited with impending menstruation, and (d) due to persistent corpus luteum. The gravity of the condition depends on the type. Women who have never menstruated may nevertheless ovulate and their sex tract undergo cyclic changes. Our test, when positive, permits of the determination of sex. Sterilities probably fall into two classes, the first with normal cycle, the second with depressed function. In the first group other factors besides ovarian function must be taken into account. Death of the fetus after the twelfth week can be recognized by the blood test.—R. G. H.

**Further experiments on hermaphroditism in the presence of an intact testis** (*Nouvelles expériences sur l'hermaphroditisme expérimental en présence de testicules intacts.*) Lipschütz, A., *Compt. rend. Soc. de biol.* 97: 1401-1402. 1927.

Ovarian transplants into male guinea pigs, each with one testis intact, produce evidences of feminization in from five to nine weeks when tried in Chile. In North Europe these same results take five to eight months to develop.—J. C. D.

**Impregnation by a guinea pig rendered hermaphroditic** (*Fécondation par le cobaye expérimentalement hermaphrodite.*) Lipschütz, A., and E. Vinals, *Compt. rend. Soc. de biol.* 97: 1400-1401. 1927.

Two males with intact testes were feminized by ovarian transplants. The mammary glands were actively secreting. At this time they impregnated three normal females.—J. C. D.

**On the occurrence of the oestrous cycle after x-ray sterilization. Part III. The periodicity of oestrous after sterilization of the adult.**

Parkes, A. S., Proc. Roy. Soc. B, 101: 421-449. 1927.

The length of pretreatment (control) cycles is compared with the length of cycles after x-ray sterilization in more than 60 animals. The periodicity of oestrous was not significantly affected by x-ray elimination of the follicles and corpora lutea. The variability of the post-irradiation cycle was greater than that of the pre-irradiation cycle.—E. A.

**Ovum and hormones.** Zondek, B., and S. Aschheim, Klin. Wchnschr. 6: 1321-1322. 1927.

The paper deals with several questions, fundamental to gynecology on the basis of a large series of well considered experiments carried out on the mouse. 1. What happens when the ovum is destroyed? In corroboration of the work of Parkes, it is found that radiation of the ovaries in sufficient dosage to destroy every vestige of ova and follicles does not prevent the recurrence of oestrous cycles, a result that seems to support Steinach's theory of the function of the interstitial tissue. 2. Does ovarian hormone cause ripening of the ovum? Injection of folliculin into infantile females causes oestrus changes in uterus and vagina, but no immediate ripening of ova. 3. Finally, what happens if hormone production is inhibited? Females fed thorium have ripe Graafian follicles, but show no oestrus and no changes in the genital tract; but if anterior hypophyseal extract is injected along with the thorium the animal goes into heat. Hence the anterior lobe hormone is the "motor" that sets the oestrous mechanism going by acting through a responsive ovary. Ovum and ovarian hormone are, therefore, coördinated, but not causally related, and both are under the control of the pituitary.

—Carl Hartman.

**The so-called pars intermedia of the human hypophysis (Über die sogenannte Pars intermedia der menschlichen Hypophyse).** Dayton, T. R., Ztschr. f. Anat. u. Entwicklungsgesch. 81: 359-370. 1926.

From an examination of over 100 normal adult human hypophyses and some from infants, the author concludes that in the human adult there is no true pars intermedia. Either the anlage of pars intermedia of the embryo disappears entirely or, what is more probable, has become something quite different, namely, mucous glands, which can be seen in children, but not in adults, or small basophilic cells. The stratified epithelium between the lumen

of Rathke's pouch and posterior lobe during later development becomous glands, which can be seen in children but not in adults, or the growth of the pouch or stops growing entirely. From the fact that the cells about the colloid vesicles may be exactly the same in structure as those of the anterior lobe, and in pregnancy, castration, and certain pathological changes in the reproductive glands (a case of his own is described) may show the same changes as occur in the anterior lobe cells proper, the author thinks that all of the colloid vesicles are derived from the anterior lobe. Occasionally there are small areas where the epithelium of the vesicles is ciliated.—A. T. R.

**Note on the mechanism of pituitary hyperglycemia** (*Sur le mécanisme de l'hyperglycémie hypophysaire*). Nitzescu, I. I., and P. Ramneantu, *Compt. rend. Soc. de biol.* 97: 1105-1106. 1927.

If the blood sugar level of the arterial blood entering a muscle is compared with that of venous blood leaving it, the level in the venous blood is lower normally, but higher following injections of posterior lobe extract.—J. C. D.

**The peduncle of the human hypophysis** (*Sul peduncolo dell'ipofisi umana*). Orlandi, N., *Rev. sud-am. de endocrinol.* 10: 839-896. 1927.

An extensive anatomico-pathological study of the peduncle of the hypophysis is given, including tuber cinereum, infundibulum, pars nervosa and pars linguiforme (pars tuberalis). The following are among the important conclusions. The pars nervosa of the peduncle contains nerve fibers which arise from nuclei in the tuber cinereum and go to end in the neurohypophysis. During their course they give fibrils to vessel walls and to the epithelium of the pars linguiforme (tuberalis). The supporting tissue of the peduncle is represented by microglia and the rare elements of fibrous neuroglia. The capillaries of the peduncle are typically sinusoidal. They have a characteristic precollagenous reticular tissue adventitia, but no membrane of Held. The "gitterfasern" is found in the pars linguiforme and merely surrounds the vessels in the pars nervosa. Different types of pigment cells are described. In pregnancy the peduncle does not show any changes of note other than a predominance of cells with dark nuclei in the pars linguiforme during the latter months of gestation. In cases of chronic nephritis the vessels of the peduncle contain a homogeneous lipid substance arising from the prehypophysis, probably in conjunction with the increase of basophil elements. Inflammatory processes of the meninges, either acute or chronic, seldom affect the peduncle. In some cases of diabetes mellitus and in polysarcia there is an infiltration of lymphocytes in the peduncle and the tuber cinereum. Cysts have been observed which have arisen from degeneration in the center of nodes of pavement epithelium and from dilatation of the tubules of the

pars linguiforme. The hypophysis is frequently the site of neoplastic metastases. In conclusion, the author expresses the conviction that the several parts of the peduncle and the hypophysis constitute a system and that histopathological researches in this region must be considered incomplete if they fail to take cognizance of all the parts of this system.—W. J. A.

**Oxytocic power of pituitary under different circumstances (Der Gehalt des Hypophysenhinterlappens an uteruserregender Substanz unter verschiedenen Bedingungen).** Pak, C., Arch. f. exper. Path. u. Pharmakol. 114: 354-361. 1926.

After removal of the ovaries in rats the uterus was less inclined to spontaneous contraction, but the potency of the pituitary extract in oxytocic principle was not decreased. Thyroidectomy, arsenic poisoning, CO-poisoning, and intensive Röntgen irradiation were all ineffective. After  $HgCl_2$  and diphtheria toxin poisoning and to some extent after thyroid feeding, the oxytocic potency of extracts was decreased. Faradization of the cervical sympathetic produced an increase in four out of five instances.—C. I. R.

**Report of a case of diabetes insipidus.** Peabody, F. W., Tr. A. Am. Physicians, 40: 170-176. 1925.

The case reported occurred in a white woman, 61 years old. The diagnosis of diabetes insipidus in this case was based upon the sudden appearance of great thirst, polyuria, and the excretion of a urine with a specific gravity which, although not quite so low as that commonly seen in this condition, approximated it; on the evidence of the inability of the kidney to concentrate the urine, as shown by the 2-hour test; and on the decrease of urinary output with increase of the specific gravity of the urine following the injection of pituitrin. The disease lasted four years and was characterized by alternating cycles of several months' duration. There was, however, a gradual tendency to improvement, so that while she was almost confined to the house during the first year, she was able to travel in the last year. Having passed through the series of remissions and relapses, she seemed to have reached a state of comparative relief from diabetes insipidus at the time when she developed another and fatal condition apparently unrelated to it. The most interesting clinical problem involved was that of the etiology. The usual causes of the symptom-complex of diabetes insipidus—tumor, syphilis, tuberculosis, fracture of the skull, or cerebral hemorrhage in the ordinary sense—could apparently be excluded, and, while no definite proof could be offered, the almost simultaneous onset of the diabetes insipidus and the hemorrhagic tendency led the majority of the many physicians who considered the case to regard the diabetes insipidus as the result of a small hemorrhage which happened to take place in the substance of the hypophysis. The occurrence of the bleeding

into the vitreous of the eye shows that in the hemorrhagic condition from which she suffered the bleeding was not limited to the subcutaneous tissues, and the pathological condition of the hypophysis as revealed at autopsy might well be explained on the basis of hemorrhage. The fact that no similar case has been reported in the literature gives to this instance a special significance.—I. B.

**Glycemia, glycogen. and the action of insulin in decapsulated rats** (*La glycémie, le glycogène et l'action de l'insuline chez les rats décapsulés*). Artundo, A., *Compt. rend. Soc. de biol.* **97**: 411-413. 1927.

The glycemia falls slightly three to eight days after removal of the adrenals, rises somewhat above normal at two weeks, and becomes normal at five weeks. The liver glycogen is decreased up to eight days, increased at two weeks, and normal at five weeks. The muscle glycogen is increased at three days, reduced at fourteen days, and normal at five weeks. The operated animals were very susceptible to insulin at two weeks, and less so at five weeks, though more so than the controls. In them the insulin reduced the liver glycogen regularly and the muscle glycogen less regularly.—J. C. D.

**Acetates in normal and diabetic blood** (*Les Acetates dans le sang normal et diabetique*). Bruno, A., *Compt. rend. Soc. de biol.* **97**: 1512. 1927.

In normal dogs there are 1 to 1.5 mgm. of acetic acid per 100 cc. of blood. This is increased in diabetes and reduced under insulin.—J. C. D.

**The fate of sugar in the animal body. IV. The tolerance of normal and insulinized rats for intravenously injected glucose and fructose. V. A seasonal occurrence of ketonuria in fasting rats accompanied by changes in carbohydrate metabolism.** Cori, C. F., and Gerty T. Cori, *J. Biol. Chem.* **72**: 597-625. 1927.

The intravenous glucose tolerance of non-fasting male rats is at a rate of infusion of 2.5 gram per kgm. of body weight per hour. An identical value has been obtained on rats fasted previously for 48 hours. The intravenous tolerance limit of mice is close to 2.5 grams of glucose per kgm. per hour. The absorption of glucose from the intestine of the mouse proceeds at a rate of 4.6 grams per kgm. per hour and leads to glycosuria. In the rat, the rate of absorption of glucose from the intestine is lower than the intravenous tolerance rate. The tolerance of fasting rats for fructose, when infused into the femoral vein, is at a rate of 0.35 gram per kgm. per hour. However, for an infusion into a mesenteric vein, the tolerance limit is at a rate of 0.7 gram per kgm. per hour. In non-fasting rats, the tolerance limit is at a rate of 0.65 gram of fructose per kgm. per hour. When glucose or fructose is infused above the

tolerance rate (4.5 grams per kgm. of rat), there is no marked difference in the rate of utilization of these two sugars. Large doses of insulin raise the intravenous glucose tolerance from 2.5 to 3.0 grams per kgm. per hour, or by 20 per cent. Normal rabbits show an intravenous tolerance rate of 0.9 gram of glucose per kgm. per hour. After insulin treatment the tolerance increases to 1.3 grams per kgm. per hour or by 40 per cent. Insulin is without effect on the tolerance for intravenously injected fructose.

Rats, during the summer months, excrete from the 24th to the 48th hour of fasting an average of 6.2 mgm. of total acetone bodies per 100 grams of body weight per 24 hours. During the winter months the excretion of acetone bodies was only 1.9 mgm. per 100 grams per 24 hours. When rats were kept for 3 weeks in winter at a room temperature comparable to that of the summer, the excretion of acetone bodies did not rise, showing that the summer heat is not directly responsible for the occurrence of ketosis in fasting rats. The intravenous glucose tolerance of rats suffering from summer ketosis was at a rate of 1.6 grams per kgm. per hour. This is 36 per cent lower than the values obtained in winter on rats without ketosis (see the preceding abstract). The lower glucose tolerance was due to a lessened ability of the tissues to oxidize glucose, while the glycogen storage in the tissues was not changed. From 721 grams of glucose that were absorbed in 4 hours by the rats in summer, 131 mgm. were oxidized, while 380 mgm. were converted into glycogen. In winter, for an almost equal glucose absorption, the oxidation and glycogen formation amounted to 281 and 388 mgm., respectively. Insulin injected into rats suffering from summer ketosis increased the amount of glucose oxidized. It is concluded that ketosis is associated with a reduced functional activity of the pancreas and, in consequence of this, with a reduced capacity of the tissues to oxidize glucose.—C. F. Cori.

**The management of diabetes mellitus associated with pulmonary tuberculosis.** Elliott, C. A., and W. H. Nadler, *Med. Clin. N. A.* 9: 1453-1472. 1926.

Because of the conflicting indications in the dietary treatment of diabetes and phthisis, the combination of the two diseases was formerly regarded as fatal. The use of insulin has made it possible to meet the requirements of both conditions, and as a result of the better management of diabetes. The prognosis of cases complicated with tuberculosis has been greatly improved. Four case histories illustrate this point. Normal glycemia favors the healing of tuberculous lesions; hyperglycemia predisposes to their extension.—I. B.

**Glycemia as a practical guide in the treatment of diabetes mellitus.** Elliott, C. A., P. Starr, and W. H. Nadler, *Tr. A. Am. Physicians*, 40: 316-320. 1925.

The occurrence of frequent fluctuations in the general level of blood sugar in diabetes mellitus is emphasized. The maintenance of normal glycemia is emphasized as essential to efficient diabetic treatment. A procedure making possible the continual supervision of the blood-sugar level in patients with diabetes is described and illustrated.—I. B.

**Clinical problems in the management of diabetes with a review of four fatal cases.** Fitz, R., *Med. Clin. N. A.* 10: 1163-1174. 1927.

In order to discuss a few phases of the problem of diabetes, the author describes in detail two cases of diabetes with tuberculosis, one with duodenal ulcer and one with marked tonsillar infection. Tuberculosis as a complication of diabetes is frequent and often overlooked. X-ray examinations of the chest in diabetic patients are advocated. All discoverable foci of infection should be given prompt attention. A careful physical examination of each case of diabetes should be made at least twice a year, as normality of weight, general appearance and blood and sugar determinations do not necessarily exclude serious complications. Education of patients on the diabetic question is vital. Finally, the physician undertaking the care of a diabetic patient must be properly equipped in the management not only of the physical, but also of the mental aspects of the individual.

—I. B.

**Demonstration by pancreatic transplantation of the control of the internal secretion of the pancreas through hormones.** Experiments on normal animals (*La régulation de la sécrétion interne pancréatique par un processus humoral, démontrée par des transplantations de pancréas. Expériences sur des animaux normaux*). Gayet, R., and M. Guillaumie, *Compt. rend. Soc. de biol.* 97: 1927. 1613-1614. 1927. Experiments on depancreatized animals (*Expériences sur des animaux dépancréatés*.) *Ibid.* 1615-1618.

Experiments on one normal and three depancreatized dogs are reported. The pancreas from a donor was transplanted into the carotid jugular circulation of a recipient. The blood sugar was followed over a period up to two days. In normal dogs the transplant did not influence the blood sugar. In depancreatized dogs, which were markedly hyperglycemic, introduction of the transplant was followed by a steady fall of blood sugar to a normal level. When the transplant was removed, the blood sugar rose again to a pathological level.—J. C. D.

**An unusual case of diabetes mellitus: death after thirteen years' observation; necropsy.** Gordon, A. H., C. L. Connor and I. M. Rabinowitch, *Am. J. M. Sc.* 175: 22-31. 1928.

A case of diabetes mellitus is reported. The patient was under observation for thirteen years, during which time complete records



of clinical and metabolism findings were kept. This case demonstrates that, in spite of a very clear history, it does not necessarily follow that diabetes following repeated attacks of gall-bladder disease is due to the latter. This may explain the failures at times of surgery to alleviate or improve diabetes when associated with disease of the biliary passages. This case also emphasizes the fact that the clinical picture (the attitude, expression, color, nutrition, etc.) is not a reliable index of progress of insulin-treated diabetics. Blood analyses are here indispensable. This patient appeared to be well nourished and felt well. The post mortem findings, however, showed that the skin did not contain fat, but water. Also because of the long duration of the disease and the arteriosclerosis, other evidence of active diabetes (glycosuria) was masked. The patient had a raised renal threshold for sugar. This case is also another demonstration of the relationship between the cholesterol content of the blood and prognosis. The differential diagnosis during the final stages of the disease was difficult, because of a combination of findings not uncommon, but not frequently mentioned in the literature. Cerebral manifestations of diabetic coma may simulate those of uremia or cerebral hemorrhage. Suppression of urine, albumin and casts, high blood urea and creatinin, leukocytosis altered reflexes and fever were all present in this case. Other clinical features of interest were the presence of insulin edema, the color of the skin and the absence of response to insulin. The pancreas and the blood vessels of the brain were the organs of special interest in post mortem.—Author's Abst.

**Results of prolonged treatment of normal animals with insulin** (*Récherches expérimentales sur le traitement prolongé des animaux normaux par l'insuline*). Hornung, S., *Compt. rend. Soc. de biol.* 97: 1500-1502. 1927.

Dogs show a decreasing influence of insulin on the blood sugar.  
—J. C. D.

**Adiposity and other etiological factors in diabetes mellitus.** Anders, J. M., and H. L. Jameson, *Tr. A. Am. Physicians*, 40: 230-245. 1925.

From statistical studies it appears that the death-rate from diabetes in Philadelphia had been increasing steadily until checked by the use of insulin about the middle of 1923, and that the incidence in patients under the authors' personal observation has been increasing steadily up to the end of 1924. Whereas in 1913, the numerical rating of diabetes as a cause of death assigned it to 22nd place, 10 years later it occupied 12th place, corresponding with what was found in the Registration Area of the United States and in New York in 1920. After the age of 40, women showed a decidedly higher diabetes death-rate and heavier incidence than men during

the past two decades, while for the like preceding period, the preponderance of deaths from this complaint occurred in males. This change in the influence of the sexes upon the mortality rate is inexplicable. In the authors' series of 1306 cases of adiposity, which includes 119 cases of diabetes, this sex relationship was also noted with respect to the incidence of the disease. The excess of deaths among females has progressively increased in Philadelphia in recent years until the sex ratio reached approximately 2 to 1 in favor of females. The predominant effect of adiposity as a predisposing cause of diabetes is clearly indicated by interesting tables. Only 1 in 12 obese subjects develop diabetes among Gentiles, and 1 out of every 8 among Jews. Whether the higher ratio among the Jewish race is owing to greater susceptibility to the disease or a relatively great degree of overweight alone, as Joslin believes, is perhaps an unsettled question. The phenomenal rise in the diabetes death-rate and incidence among women in recent years is not due solely to their greater and more general adiposity. The cases of diabetes have multiplied themselves five times since 1880; but it cannot be justly claimed that overweight has increased in degree to a like extent. Finally, in 18 per cent of this series the disease occurred in persons of normal or even subnormal weight.—I. B.

**Diabetic coma and its treatment.** Joslin, H. F., and Priscilla White, *Med. Clin. N. A.* 10: 1281-1305. 1927.

Coma and cancer caused 6 deaths among the 1,138 diabetic patients seen by the authors during the year ending July 1st, 1926. Forty-five of the living group of 200 or more children have already had coma 53 times; in 9, diabetes was discovered during coma. Coma is today as dangerous as ever, but far less fatal; but 10 per cent of the authors' fatalities last year were due to coma. Coma is preventable. The danger of the alkali treatment of diabetic coma is now supported by clinical evidence in the possibility of occurrence of alkalosis following recovery from coma in patients to whom no alkalies were given. We must differentiate between diabetic coma, coma due to hypoglycemia, and coma caused by renal block with retention of non-protein nitrogen, as well as other conditions associated with coma.—I. B.

**Insulin, blood pressure, and vagus tonus (Insuline, tension artérielle et vagotomie).** Jung, L., and L. Auger, *Compt. rend. Soc. de biol.* 97: 1163-1164. 1927.

There was a decrease in the response of the heart to vagus stimulation when tested by the eye heart reflex, as the blood pressure fell following insulin injection in dogs.—J. C. D.

**Glucose as a physiological excitant of the internal secretion of the pancreas (Le glucose excitant physiologique de la sécrétion interne**

du pancréas). Képinov. L., and Petit-Dutaillis, *Compt. rend. Soc. de biol.* **97**: 1597-1598. 1927.

Deprancreatized dogs were kept in carbohydrate equilibrium by small pancreatic grafts. Injections of glucose resulted in a protracted elevation of the blood sugar level instead of an elevation followed by reduction below normal, found in animals with the pancreas intact.—J. C. D.

Does the nervous system influence the supply of insulin under normal conditions? (*Le système nerveux intervient-il dans la régulation de l'insulinémie physiologique?*). LaBarre, J., *Compt. rend. Soc. de biol.* **97**: 1184-1187. 1927.

Vascular anastomosis between two dogs was established. The vagi of the donor were cut. The pancreas of the recipient had been removed. The hyperglycemia of the recipient was not modified. Similar results followed when the donor's pancreas was entirely isolated. If the nerve supply to the donor's pancreas was left intact, the blood sugar of the recipient is reduced. The secretion of insulin is therefore dependent on the vagus nerve.—J. C. D.

Increased insulin output following injection of posterior hypophysis extract (*Hyperinsulinémie consécutive à l'injection d'extrait hypophysaire postérieur*). La Barre, J., *Compt. rend. Soc. de biol.* **97**: 1416-1419. 1927.

The experiments were tried on dogs deprived of their adrenals.  
—J. C. D.

A relationship between body temperature and blood sugar in rabbits. Lawrence, R. D., *J. Physiol.* **63**: 12-13. 1927.

An account of an observation that in rabbits a spontaneous rise in blood sugar was accompanied by a lowering of body temperature by as much as 5° F. in some cases. This phenomenon was observed in only seven out of 100 rabbits and usually occurred when animals were excited. The author suggests that this is an adrenalin reaction produced sometimes by excitement, sometimes as a reaction to the fall in blood sugar produced by insulin and sometimes as a reaction to collapse of undetermined origin. This suggestion is supported by the fact that the hyperglycemia occurring in rabbits when temperature is lowered is prevented by bilateral splanchnectomy and by the fact that ergotamine will prevent the increase. As a precaution the author suggests more than one preliminary test in determining the influence of a substance on blood sugar of rabbits.—C. I. R.

The state of blood sugar and adrenalin skin reactions after quartz-mercury vapor lamp irradiation and after sun baths (*Das Ver-*

Schweiz. med. Wehnschr. 57: 759-761. 1927.

halten des Blutzuckers und der Adrenalinquaddel nach Quartzlampenbestrahlung und nach Sonnenbädern). Messerle, N.,

An investigation of the effects of two kinds of irradiation on blood sugar, alimentary hyperglucemia and on the reactions of the sympathetic nervous system. Twenty human subjects were used. After fasting over night, 20 grams of glucose were ingested and the glucemia curve determined during 90 minutes, after which subjects received 30-minute sun baths or 16-20-minute mercury vapor lamp irradiations at 60-80 cm. After 16-20 hours the glucemia curve was again determined. Fasting glucemia was diminished 16-20% and the glucemia curve leveled off after both kinds of irradiation, but the latter was more effective. In case of 4 subjects markedly pigmented from previous phototherapy, this treatment produced no such effects until the duration of irradiation was increased. In an attempt to determine the effect of irradiation on the sympathetic nervous system, intracutaneous injections were given of 0.1 cc. of 1:1,000,000 adrenalin, 30 minutes, 3 hours and 20 hours after irradiation. Wheals appeared in 5 minutes and reached their greatest diameter in 15 minutes and persisted to 30 minutes, after which there was recession. There was no noticeable difference in the reaction after each kind of irradiation. As compared to controls, the reaction was always more pronounced following irradiation, even as long as 20 hours after. These results, the author interprets as indicating that irradiation decreases tonus and irritability of the sympathetic nervous system.—C. I. R.

Pregnancy and diabetes. Parsons, Eloise, L. W. Randall and R. M. Wilder, Med. Clin. N. A. 10: 679-688. 1926.

Diabetic women usually do not become pregnant. Gonadal atrophy in diabetics of both sexes with associated functional deficiency is common. The danger of pregnancy to diabetic women is grave and has been regarded as an indication for therapeutic abortion. It is doubtful whether patients with severe diabetes ever survived pregnancy in the pre-insulin era. The authors report in detail their series of 11 cases of pregnancy in diabetic women; one with very mild diabetes of 17 years' duration had three pregnancies and three children; the pregnancies of the other ten women resulted in five children, two still births, and four miscarriages. In two of the patients suffering with moderately severe diabetes pregnancy was successfully completed. These young women had been treated previously for severe acidosis and depended largely on insulin when they later became pregnant.—I. B.

Insulin-thyroid antagonism. Rosenberg, M., Klin. Wehnschr. 6: 631. 1927.

The author studied the effect of insulin on glycosurias in pure hyperthyroid cases and glycosurias due to thyroid administration, and those produced by thyroid administration to diabetics. In non-diabetics he finds that insulin does not appreciably lower the sugar output; in diabetics, glycosuria is induced by thyroid extract, and this promptly responds to insulin. The author thinks that in diabetics the insulin and thyreoidin are directly antagonistic and that the thyreoidin affects the carbohydrate metabolism in a diabetic directly by a synchronous hypofunction of the islands, and that this action is different than that in a non-diabetic. In a case of mild diabetes and one of glycosuria innocens, very large doses of insulin had to be used in order to diminish the glycosuria.—H. J. J.

Ocular disturbances in diabetes. Ruedemann, A. D., *Ann. Int. Med.* 1: 39-43. 1927.

A clinical discussion of the ocular disturbances in diabetes. (No bibliography.) The author emphasizes the importance of examining the blood for the loss of vision of unknown origin. Hyperopia and myopia also may be present. Weakness or paralysis of the muscles supplied by the third nerve are most frequently encountered. Retinitis and iritis are also frequently associated with diabetes.—E. L.

Diabetes and pregnancy. Strouse, S. and P. A. Daly, *Med. Clin. N. A.* 9: 1491-1497. 1926.

Though sugar is frequently found in the urine of pregnant women, diabetes mellitus as a complication of pregnancy is comparatively infrequent. Four cases of diabetes complicating pregnancy are detailed. Individualization in the treatment of these patients is vital. Pregnancy may upset the metabolic balance in an otherwise normal woman to the extent of producing a temporary clinical picture of diabetes, and may require mere dietary adjustment to tide her through pregnancy to normality. If, however, an already severely diabetic woman becomes pregnant, insulin treatment may be necessary to enable her to take the required calories under existing needs.—I. B.

Insulin and the treatment of juvenile diabetes mellitus. Toverud, K. U., *Norsk Mag. f. Laegevidensk.* 88: 956-1010. 1927.

The author studied forty-seven children with diabetes mellitus. Most of these were patients at the Riks Hospital and some of them were under observation as long as four years. Only 17 per cent of the children had diabetes in their family; but diabetes followed acute infections in 26 per cent. The diet was based on the patient's carbohydrate tolerance. Three grams of protein was given for each kilo of body weight in children under seven years of age, and 2

gms. per kilo in the older ones. When the keto-antiketonik ratio exceeded 1.75 —1, symptoms of acidosis usually developed. It is concluded that diabetic children should have three daily injections of insulin, in order to keep their blood sugar approximately normal. When severe diabetes was present, or when the disease was chronic, it was possible to keep the blood sugar level normal during the day, but the level rose steadily during the night. The children developed normally, both physically and mentally. The carbohydrate tolerance remained stationary and even increased in seven children. These were very faithful to their diet and suffered from relatively few acute infections. In the other cases the tolerance decreased, either because of laxity in the diet or because of severe frequent infections, or both. The mortality was 36 per cent. Five of the children died in coma brought about by acute infections. One died after a fracture of the hip. In four cases the parents refused the insulin treatment, and in the other seven the diet was broken continually and the administration of the insulin was very irregular.—Daniel J. Glomset.

**Permeability of the peripheral tissues for dextrose in epinephrin diabetes (Ueber die Glukosepermeabilität der peripheren Gewebe beim Adrenalindiabetes).** Wiechmann, E., *Deutsches. Arch. f. klin. Med.* 154: 296-304. 1927.

The author has shown experimentally that the sugar content of arterial and venous plasma runs parallel, being in a fasting individual somewhat lower in the venous plasma. Forty to fifty minutes after an intake of 100 grams of glucose by mouth this difference is increased; 60 minutes after injection of 1-2 mgm. adrenalin, in spite of a marked hyperglycemia, this difference between arterial and venous blood is nearly the same as in fasting blood. In the first case the difference is 4 times as large as in fasting blood, whereas after adrenalin it is but 1.2 times as great. The same figures apply to whole blood sugar determinations. The author thinks that the sugar exchange between plasma and erythrocytes does not explain the finding, but that the permeability of the tissues for glucose is lowered through adrenalin; in this sense the adrenalin diabetes is identical with clinical diabetes, for in both the glucose-permeability of the peripheral tissues is lowered.

—H. J. J.

**Hyperthyroidism, myxedema and diabetes.** Wilder, P. M., *Tr. A. Am. Physicians*, 41: 113-146. 1926.

In a study of a series of 38 cases of diabetes mellitus combined with varying degrees of hyperthyroidism and in one case with myxedema, the author concludes as follows: The association of diabetes with hyperthyroidism occurs in about 1.1 per cent of all

cases of hyperthyroidism. Exophthalmic goiter is less frequently complicated by diabetes than adenomatous goiter with hyperthyroidism. Alimentary glycosuria is far more frequent, but is not included in these observations. Symptoms of hyperthyroidism may be obscured by those of diabetes, especially in severe acidosis or diabetic coma. One must be on guard for hyperthyroidism in all cases of diabetic acidosis. A mild diabetes may become severe by hyperthyroidism, and hyperthyroidism in crisis may provoke coma in a diabetic patient. The requirement of insulin is increased by hyperthyroidism. Iodin therapy in subjects of both exophthalmic goiter and diabetes reduces the intensity of the latter, but this drug does not influence the diabetes in patients with toxic adenoma. Iodin has no effect in uncomplicated diabetes. Thyroidectomy is usually followed by improvement in diabetes complicating hyperthyroidism. Operation in these patients is, however, more hazardous. It seems that at lower metabolic rates the tissue cell is capable of utilizing a given quantity of glucose with less insulin, and that with higher metabolic rates the requirement of insulin is disproportionately increased.—I. B.

**Studies in calcium and carbohydrate metabolism. I. Calcium and glucose tolerance in diabetes mellitus.** Wishnofsky, M., J. Lab. & Clin. Med. 13: 133-138. 1927.

A review is given of the relationship between calcium and carbohydrate metabolism. There occur simultaneously changes in calcium and carbohydrate metabolism in diseases of the adrenals, thyroid, parathyroids, and pituitary glands. This is also true in various miscellaneous pathologic states such as: pregnancy, changes in H-ion concentration of the blood, diureten and phloridzin glycosuria, pneumonia, tuberculosis, and other infectious diseases. Many observers have found a negative calcium balance in diabetes mellitus. Both Von Moraczewski and Kahn observed that the administration of calcium ameliorates the diabetic state. Employing the glucose tolerance test as an index of the severity of diabetes, the author concludes that calcium in no way improves the ability of the diabetic to metabolize glucose.—Author's Abst.

**Cause of hyperinsulinemia in the pancreatic vein following dextrose hyperglycemia** (Sur les cause de l'augmentation de la teneur en insuline du sang veineux pancréatique lors de l'hyperglycémie provoqué par injection de dextrose). Zung, E. and J. LaBarre, Compt. rend. Soc. de biol. 96: 708-710. 1927.

Dogs were used. The pancreatic vein of a donor was connected with the jugular vein of a recipient who had previously been adrenalectomized. The blood sugar level was followed in the recipient and regarded as a measure of the insulin received by way

of the pancreatic vein of the donor. With both vagi intact, injection of sugar into the blood of the donor produces insulin in the pancreatic vein. Less insulin is produced if the right vagus is cut. If both vagi are cut or paralyzed with atropin, insulin does not appear.—J. C. D.

**Topography of the parathyroids in swine** (*Zur vergleichenden Anatomie der branchiogenen Organs II. Zur Topographie der Epithelkörperchen beim Schwein, mit besonderer Berücksichtigung der Eignung des Schweins für die Gewinnung organotherapeutischer Epithelkörperchenpräparate*). Arndt, H. J., *Ztschr. f. Anat. u. Entwicklungsgesch.* 81: 191-197. 1926.

No parathyroids could be found in swine by macroscopic means. Many small masses in the neighborhood of the thyroid proved to be either accessory thyroids or lymph nodes. Microscopical examination of serial sections of the entire cervical region of fetal pigs and one pig a few days old revealed regularly one pair of parathyroids in the anterior horns of the thymus near the salivary gland. Adult pigs were not examined microscopically. The thymus extends unusually high into the cervical region in the pig. In the case of one young suckling pig the parathyroid gland on one side was not entirely surrounded by thymus tissue. In no case were the parathyroids in or near the thyroid. Apparently it is almost a hopeless task to get pure parathyroid extract from swine material. On the other hand, the pig thyroid is suitable as a source of parathyroid-free thyroid extract. No oxyphile cells nor colloid were seen in the parathyroids.—A. T. R.

**Metabolic effect and clinical application of Collip's parathyroid hormone** (*Stoffwechselwirkung und klinische Verwendbarkeit des Epithelkorperschenhormons [Collip]*). Brehme, T. and P. Gyorgy, *Jahrb. f. Kinderh.* 118: 143-178. 1927.

An exhaustive study was made of the blood, urine, and stools in normal and tetanic children. The administration of Collip's hormone in non-tetanic as well as in tetanic children is followed by an increase in calcium, a slight lowering of the Phosphorus content and a shifting of the blood reaction to the acid side, with, however, an unchanged alkali reserve. The characteristic findings in the urine during the administration showed in normal infants an increase in titratable acidity with an increase in the calcium and phosphorus excretion. The values of the organic acids and nitrogenous elements were increased. The total calcium and phosphorus were not increased in two cases of puerile tetany after the administration. The effect of parathyroid extract is not constant as in some cases of tetany the results did not coincide with others. One case of tetany which could not be benefited by intensive antirachitic



treatment was improved by parathyroid extract. The authors conclude that the ordinary tetany of infancy is not of parathyroid genetic nature and the administration of this extract is not in the form of substitution therapy. The inconstant effect of the extract in addition to the occasional appearance of coincidental hypercalcemia symptoms (pallor, vomiting, abnormal stools, apathy, drowsiness, disturbed circulation, nephritic disturbances and sometimes death) speaks against the general application of the parathyroid hormone.—M. B. G.

**Parathyroid extract in infantile tetany, report of a case.** Gibson. A. H., *Am. J. Dis. Child.* 34: 835-841. 1927.

Four cases of infantile tetany were treated with parathyroid extract (Collip), the dosage being that recommended by Hoag and Rivkin—5 units per kilogram of body weight for each milligram of rise in serum calcium desired. The total dose was administered in equal fractions hypodermatically at 4 to 6 hour intervals over a period of 24 to 36 hours. In 3 cases the rise in calcium and phosphorus was definitely related to the recovery from infection as evidenced by the drop in temperature and apparently not related to the treatment with the extract. In one case the temperature remained high and the serum calcium and phosphorus values failed to rise on administration of parathyroid extract. This case was complicated by thymic enlargement which was diagnosed by necropsy and was probably incidental. The cases reported are too few from which one can draw general conclusions as to the value of parathyroid extract in the treatment of infantile tetany. It is unwise to rely entirely on the extract to the exclusion of other better accepted methods of treatment in infantile tetany until the parathyroid extract treatment is more firmly established on sound clinical bases.—M. B. G.

**Relation of calcium and phosphorus in blood of parathyroidectomized dogs.** Reed, C. I., R. W. Lackey and J. I. Payte, *Proc. Soc. Exper. Biol. & Med.* 25: 136-137. 1927.

In normal dogs, the Ca:P ratio in the blood varies from 1.5 to 2. After parathyroidectomy the ratio is reduced until at the first appearance of tetany the ratio is approximately 1.0. The change is due both to decrease in calcium concentration and to increase in inorganic phosphorus concentration.—Author's Abst.

**Extirpation of the pineal gland and gonads** (*Eperimentale Untersuchungen über die Doppelextirpation der Epiphyse und der Keimdrüse*). Yohoh, A., *Ztschrft. f. d. ges. exper. Med.* 55: 349-370. 1927.

After operations performed on male chicks 30 to 40 days old the following results were noted: Extirpation of the pineal gland

is followed by a noticeably accelerated body growth accompanied by abnormal growth of the testes and a precocious development of the comb. The abnormal growth of the testes may be noticed as soon as 8 days following operation. When both the pineal gland and the testes are removed body growth is noticeably slowed and there is no perceptible growth of the comb. Following the double operation there is atony of the entire body, but this condition does not persist. The pituitary, especially the anterior lobe, becomes twice as large as normal. There are few basophiles, but the acidophile cells of the pituitary increase in number and are hypertrophied. Other internally secreting glands show a slight hypertrophy but all other organs display a growth which parallels the general body growth. The thymus gland in control animals shows regressive changes as growth progresses, but in doubly operated animals the thymus persists for a long time. It is concluded that growth of the body is dependent upon interactions between the pineal gland, the gonads and the pituitary; the pineal gland controlling the functions of the gonads and the pituitary, which in turn condition the growth of the body. The thymus also is in some manner involved.—W. J. A.

**Thymic enlargement as a cause of atelectasis.** Costello, J. P., *Med. Clin. N. A.* 11: 583-590. 1927.

This is a contention that the thymus is a direct cause of certain types of atelectasis in the newborn. The symptomatology and diagnosis are discussed, with the differential diagnosis between atelectasis and similar conditions found in the newborn. The importance of radiology in the diagnosis and treatment of thymic atelectasis is emphasized.—I. B.

**The rôle of thymus in chloroform narcosis (Die Rolle des Thymus bei der Chloroform-narkose [Tier Experimente]).** Gyorgy, E. and G. Mihalovics, *Jahrb. f. Kinderh.* 117: 248. 1927.

To determine if there is a thymic death with chloroform narcosis, white rats were separated into four groups. (1) Chloroform was administered without any further handling. (2) Thymus of a calf was injected in addition. (3) Thymus of rat was injected in addition. (4) Thymus transplanted into the rats in addition to narcosis. Normal non-narcotized rats were used as controls. The authors conclude that the treated animals stood narcosis as well as the controls and that therefore thymic death cannot be considered from a viewpoint of a thymic hyperfunction alone.—M. B. G.

**Enlarged thymus—Some observations on the physiology and anatomy of the thymus and thyroid glands.** Spohn, H., *Trans. Canadian Society for Study of Diseases of Children.* *Am. J. Dis. Child.* 34: 697. 1927.

The opinion is advanced that there are thymus belts and that these belts correspond to regions in which pathological conditions of the thymus are found. In support of this theory some statistics of comparative incidence between various regions in America are given and note made of the apparent rarity of thymus disorders in Europe. The condition has been found to be fairly frequent, however, by Feer in the neighborhood of Zurich. The observations of Berry are recalled to the effect that in every patient who died of toxic goiter an enlarged thymus was found on post mortem examination. Based upon a study of 120 cases of thymus enlargement with symptoms in which treatment was instituted, the author concludes that in the majority of instances an internal secretion rather than pressure with enlargement is responsible for the symptoms.

—M. B. G.

The early diagnosis and treatment in enlargement of the thymus gland. Sturr, R. P., *Arch. Pediat.* 44: 733-741. 1927.

Based on a study of 65 cases of enlarged thymus, the author considers that gland as either a symptom producing or non-symptom producing thymus. The local symptoms due to enlarged thymus are signs of upper respiratory infection, persistent formation of mucus in pharynx and trachea, cough, hoarseness, in crying and coughing, difficult and stertorous breathing, breath holding, cyanosis and attacks of cyanosis. General or toxic symptoms were present in 40 per cent of the cases. All suspicious cases should be given the benefit of x-ray treatment.—M. B. G.

The relation of the thyroid gland to calcium metabolism. Aub, J. C., W. Bauer, M. Ropes and C. Heath, *Tr. A. Am. Physicians*, 42: 344-345. 1927.

The relation of the thyroid to carbohydrate, fat and total metabolism has never been established. The serum calcium and phosphorus in myxedema, exophthalmic goiter, and adenoma of the thyroid are normal. The excretion of calcium and phosphorus, however, is not normal. This was established by giving a diet inadequate only in calcium, and by analyzing the excreta for calcium, phosphorus and nitrogen. Thus the minimal rate of calcium metabolism could be established. Thyroid administered to normal controls and to myxedematous patients also causes a definite increase in calcium. It is clearly seen that hyperthyroidism is associated with a very marked increase in calcium excretion. X-rays of the bones of the hand also show a diminished density in patients with exophthalmic goiter, indicating a loss of calcium. Two patients with parathyroid tetany were studied in the course of their treatment with Collip's parathyroid extract and it was clearly demonstrated in both that when thyroid extract was given in addition to constant doses of parathormone, the calcium in the blood and in

the excreta was markedly increased. From these data the following conclusions are justified: (1) The thyroid hormone influences the rate of calcium and phosphorus metabolism in a way similar to its effects on carbohydrate, fat and protein. (2) Hyperthyroidism has an effect similar to the administration of Collip's parathyroid extract in influencing calcium excretion, but it does not raise the level of normal blood calcium. (3) In tetany, due to low-blood calcium, thyroid extract raises the blood-calcium level as well as increases the calcium excretion. In this disease it is an important adjunct in treatment.—I. B.

**The effect of thyroxin on the respiratory and nitrogenous metabolism of normal and myxedematous subjects.** 1. A method of studying the reserve or deposit protein with a preliminary report of the results obtained. Boothby, W. M., I. Sandiford, K. Sandiford and J. Slosse, *Tr. A. Am. Physicians*, 40: 195-229. 1925.

The effect of thyroxin or dessicated thyroid on the various metabolic functions of the body as evidenced by changes in the respiratory metabolism and the partition products in the urine and blood, are reported on one normal and two myxedematous individuals who throughout the experimental period were eating an accurately known diet. The evidence at present available indicates that thyroxin does not cause a demonstrable change in the true endogenous protein metabolism but does cause a temporary increase in elimination of urea nitrogen, which represents apparently a decrease in the quantity of stored or deposit nitrogen during the period in which equilibrium is being established. The administration of thyroxin or dessicated thyroid to normal or myxedematous subjects on a constant protein intake, to exclude variations in the exogenous protein metabolism, provides a new method for studying the deposit or reserve protein of the body.—I. B.

**Relationship of diseased tonsils to goiter.** Bram, I., *M. J. & Rec.* 125: 442-445. 1927.

Basing his deductions upon the study of a series of 9864 goiter cases, the author urges the adoption of an open-minded attitude in the evaluation of causal relationship in the observation of goiter patients presenting diseased tonsils. The frequency with which infectious foci occur in teeth, nasal passages, sinuses, appendix, gall bladder, and uterine adnexae, must also be borne in mind. We must be conservative in our estimation of the degree of etiological responsibility of infectious foci, since the majority of these patients give a direct statement of psychic trauma as the apparent exciting cause of the syndrome. In several instances in this series the exciting cause of exophthalmic goiter appeared to be tonsillectomy itself; the patient claimed to have been in perfect health until the tonsils were removed, when nervousness, trembling, excitability,

emotionalism, and insomnia appeared, followed by loss in weight, bulging eyes and large neck. Here it is reasonable to assume that tonsillectomy served as a psychic trauma. The same might be said of nasal septum operations, appendectomy, and even ordinary dilatation and curettement of the uterus. Exophthalmic goiter following childbirth is probably not due to parturition per se, but to the psychic trauma incident to labor. The following conclusions are drawn: (1) In simple nontoxic goiter it is doubtful whether diseased tonsils play an etiological rôle. Hence, tonsillectomy, without the administration of additional therapeutic measures, usually fails to cure the patient. (2) Diseased tonsils appear to play a minor rôle in the assumption of toxicity (hyperthyroidism) by a previously nontoxic goiter. Tonsillectomy in these cases may result in a degree of amelioration of toxicity but the goiter itself is unaffected. (3) In exophthalmic goiter diseased tonsils may play a contributory etiological rôle. The major factors are apparently the predisposing neuropathic makeup of the individual, superimposed upon which a psychic trauma appears to be the usual exciting cause of the affection. Tonsillectomy in exophthalmic goiter with the expectation of curing the disease is usually disappointing; this procedure should be regarded as merely supplementary to more direct therapeutic measures. (4) Despite the frequent disappointments as to results, diseased tonsils should be removed in all goiter cases. Care must be exercised in toxic adenoma and especially in exophthalmic goiter that tonsillectomy be performed at a time when the resultant reaction would appear to be negligible.—Author's Abst.

**Hypothyroidism as a cause of intractable constipation.** Brown, T. B., *Tr. A. Am. Physicians*, 41: 162-167. 1926.

In a number of cases of intractable constipation in middle life, especially in women of obese type, there occurs a subnormal basal metabolic rate. The success of thyroid opotherapy might seem to indicate that these cases are instances of hypothyroidism.—I. B.

**Myxedema and Erb's familial muscular dystrophy** (*Zur Klinik in Pathophysiologie des Myxedems [inbesondere des gutartigen inkompletten Formen]*). Curschmann, H., *Deutsche. Ztschr. f. Nervenhe.* 98: 1-28. 1927.

A case report of a boy of 9 years of age showing an incomplete myxedema and Erb's familial muscular dystrophy. The author believes it to be a coincidental affection of both systems depending upon disturbances of the vegetative centers of the midbrain.

—M. B. G.

**Exophthalmic goiter.** DeCourcy, J. L., *Boston M. & S. J.* 197: 1305-1309. 1928.

A statement of the fundamental factors producing the characteristic signs and symptoms.—J. C. D.

**Significance of cardio-vascular methods of investigation (capillary visualization, electrocardiogram, roentgenogram) in the diagnosis of mongolianism and myxedema in children** (Die Bedeutung der Kardiovascularen Untersuchungsmethoden [Capillaroskopie, Elektrokardiographie, Rontgenographie] für die Beurteilung des Mongolismus und des Myxedems beim Kinde). Doxiades, L. and C. Pototzky, *Klin. Wchnschr.* 6: 1326-1328. 1927.

Capillary, electrocardiographic and roentgenographic observations were made on 25 mongolian idiots and 15 myxedematous children. In mature full term mongolians the capillary loops are scant but have the form of ripe capillaries, while in prematurely born mongolians they have the form of arched capillaries. The subpapillary and papillary layers are colored light yellow in both premature and full born mongolians. The normal color is rose. In premature mongolians there is a small pulse with thread like formed vessels; there is no change in the rhythm but the blood pressure is 10 to 15 mm Hg. below the normal. The heart shadow and cardiac dulness is increased in most of the cases. The electrocardiogram in mature mongolian idiots shows a typical indolent vagus heart in mature mongolian idiots and "an infantilism of the cardiovascular system" in prematures. Ip spike is greater than the Ir, the Fp deep and broad. In the myxedematous child is found scant, broad, bluish capillary loops with a grayish white subpapillary layer with wide blue plexuses. The heart is powerful, with a full pulse and normal pressure. The electrocardiogram shows a left heart preponderance, high R spike, low final wave, prolonged stimulation and tense sympathetic heart, as against the indolent vagus heart of the mongolian. The appearance of the capillaries is a gauge for therapy. A case of suspected mongolianism with a subpapillary layer simulating an endocrine picture should be given organotherapy. Arched capillaries denote poor prognosis. If the subpapillary layer does not show any changes in a case of mental delinquency, the prognosis is unfavorable and organotherapy of no avail. The results of treatment may also be checked up by observations of the cardiovascular system. The authors use thyroid and anterior pituitary extract alternately.—M. B. G.

**Results of thyroidectomy for hyperthyroidism as indicated by examination a year or more following operation.** Elliott, C. A., *Tr. A. Am. Physicians*, 41: 91-99. 1926.

This series of 74 patients operated upon is divided into two groups: One group was thyroidectomized more than a year previously and the other from 6 to 12 months prior to examination. No

discrimination was made between toxic adenoma and exophthalmic goiter. The author states that subtotal thyroidectomy arrested hyperthyroidism in 71 out of the 74 cases studied. Three of the 71 showed evidences of myxedema, which was controlled by thyroid extract. Three cases of the 74 remained slightly hyperthyroid. Permanent tissue damage was noted in 49 of the 74 cases 6 months to 6 years after operation. In 37 cases residual damage was present without symptoms, while in 12 patients partial disability was present.—I. B.

**Long-standing hyperthyroidism with spontaneous subsidence.** Eshleman, C. L., *Med. Clin. N. A.* 9: 1103-1107. 1926.

This is a report of a case in a colored woman 57 years of age who had been under observation for marked exophthalmic goiter for 14 years. The improvement noted during this period of time is regarded as spontaneous, since the author cannot associate it with any treatment. The patient, though she recovered spontaneously from the primary condition, is now regarded as a chronic cardiac case, able to carry on only a part of her accustomed duties. The author concludes that while incipient cases may become well spontaneously, this is rare in severe Graves' disease, hence this case is worthy of note. Severe cardiac damage is to be expected under the circumstances.—I. B.

**Experiments in myxedema in childhood (Versuche beim Myxedem im Kindesalter).** Geldrich, J., *Jahrbuch f. Kinderh.* 117: 247. 1927.

The influence of thyroxin on the basal metabolic rate was followed in a 14-year-old myxedematous girl who originally showed a B. M. R. of minus 25 per cent as against that of a normal girl. Thyroxin, 0.02 mgm. twice a day, was administered for 9 days. In the myxedematous girl, the rate rose 25 per cent on the first day following the administration, 50 per cent on the next day, and finally up to 70 per cent on the day after the suspension of treatment. The rate on the 18th day after the treatment had been discontinued was still 20 per cent increased. The initial rate was not reached even in one and a half months after cessation of treatment. The rate in the normal girl was increased 14 per cent, with a drop to normal by the 14th day. The author concludes that a hypothyroid child is much more sensitive to thyroxin than a normal one.  
—M. B. G.

**The management of goiter patients with congestive heart-failure.** Grant, S. B. *Med. Clin. N. A.* 11: 569-581. 1927.

Congestive heart failure in goiter patients responds to treatment far more satisfactorily than is the case in other types of cardiac disease. Especially is this true following successful thyroidec-

tomy in patients suffering with toxic adenoma. Patients of this type should undergo a period of preoperative attention in which the internist, surgeon and laboratory clinician should share the responsibility. I. B.

**The effect of acetyl thyroxin on the teeth of newborn rats.** Hocklus, Margaret M., *Proc. Soc. Exper. Biol. & Med.* 25: 55-57. 1927.

Subcutaneous injection of acetyl thyroxin into newborn white rats causes precocious development and eruption of the incisor teeth, which penetrate the epithelium three to five days before the teeth of the control animals erupt. The effect on these teeth is comparable to that produced on other parts of the body. The formation of enamel does not show a greater degree of acceleration than any other process of tooth formation. The molars of injected rats are not affected by the acetyl thyroxin.—Author's Abstr.

**Injuries to the recurrent laryngeal nerve in operations of the thyroid gland.** Kelly, T. H., and V. Wipporn, *Illinois M. J.* 51: 307-311. 1927.

When compared to the great number of thyroidectomies performed annually, injury to the recurrent laryngeal nerve is uncommon. The surgeon should examine the larynx preoperatively to determine the condition of the vocal cords, and again before the patient leaves the hospital. Unless promptly treated, the resulting dyspnea from bilateral paralysis may be fatal. However, in the case of unilateral paralysis producing hoarseness or bilateral paralysis with complete aphonia, most authorities report clinical cures within from three months to a year. Injury to the recurrent laryngeal nerve may be avoided by careful technique and by leaving a portion of the posterior part of each lobe. I. B.

**The geographical distribution of goiter.** Kerr, W. J., *Tr. A. Am. Physicians*, 12: 326-329. 1927.

As conditions in remote and uncivilized districts become known, it is apparent that no country is entirely free from goiter. The known endemic foci are in Switzerland, India, France, Italy, Germany, Russia, China, Australia, New Zealand, Africa, South America and North America. Around the Great Lakes and in the Pacific Northwest we have large areas of moderate incidence, with smaller centers where almost the whole population is affected. The author had an opportunity during the World War to study the incidence of goiter in a region covering approximately one-third of the total area of the United States, comprising the states of Minnesota, the two Dakotas, Montana, Wyoming, Utah, Idaho, Washington, Oregon, Nevada and California. The examinations were made on drafted men coming to Camp Lewis, Washington, during the second draft. Examinations were made on over 21,000 recruits at the same time of



the year, the ages ranging from 21 to 31 years. The draft quotas were known and, in general, were based upon population. The incidence in the group from each county was easily determined, which served as an index of the degree of endemicity in this large section of the country. In these examinations the author was assisted by Thomas Addis, of San Francisco, and Karl Moran, of Portland. The figures of the War Department of the United States Army suggest that exophthalmic goiter is most prevalent in regions of high incidence of endemic goiter. This is contrary to the generally accepted opinion, that the frequency of the one varies inversely with the frequency of the other. Kerr believes that the Army statistics are subject to error, in view of the general lack of knowledge of the classification of goiter among the medical profession. Many cases of large toxic goiter without eye signs were probably classified as exophthalmic goiter. There is a great variation in the incidence of endemic goiter along the sea-coast, and in certain instances it is much higher than in inland regions.—I. B.

**Exophthalmic goiter and the involuntary nervous system, XVI. The influence of subtotal thyroidectomy with and without compound solution of iodine on the course of the disease.** Kessel, L., and H. T. Hyman, *Arch. Int. Med.* 40: 623-636. 1927.

The authors' purpose is to furnish data whereby a comparison can be made between the course of exophthalmic goiter without the institution of specific therapeutic measures, and the course when subtotal thyroidectomy and the iodides are employed. A study of 129 patients was made. Of these, 69 were not submitted to operation, due to factors beyond the control of the observers, while 60 underwent subtotal thyroidectomy. Of the latter, 31 received no preoperative iodine treatment. The immediate postoperative mortality was 11 per cent, while the total mortality of the entire group of the 129 patients studied was 19 per cent. The average time of observation of these patients was approximately 24 months. The earliest case was under observation four years and the most recent 9 months. Of those not operated upon, 28 improved spontaneously. Three of the operative deaths were from the group of 31 patients who did not receive iodine solution, and 4 were from the group of 29 who were prepared with iodine. On discharge, 33 per cent of the patients operated upon declared themselves to be symptom-free for the first two years of observation. At one time or another 15 patients, or 25 per cent, had a marked exacerbation of symptoms. The remainder were benefited in such degree as to be capable of performing most of their social or economic functions. Only four patients of the group operated upon experienced a perceptible decrease in the degree of exophthalmos; in the remainder no improvement was noted, while in 11 there was a perceptible increase. The pulse rate, because of its persistent lability, could not be published

**Spontaneous decrease of goiter in Spain.** Marañón, G., Arch. de med., cir. y espec. 27: 549. 1927. Abst. J. Am. M. Ass. 90: 245.

In Spain, as well as in other countries, goiter and creatinism have decreased greatly of late without any scientific attack against the disease. In some districts, where practically everybody had goiter fifty years ago, barely four or five cases remain at present. Goiter seems to subside as living conditions improve. In the most typical Spanish focus, Las Hurdes, the communities worst affected are those at the greatest altitude, i. e., the most isolated. Food deficiency and endocrine gland disturbances act on the two great organic processes, growth and development. It seems as if in goiter cases the glands of internal secretion lack some substance necessary to the manufacture of their hormones. As the alimentary deficiency is apparently related to animal proteins, an analogy to pellagra is suggested. Other factors may intervene, but the only invariable element is undernourishment and poverty.

**An exophthalmic goiter of peculiar type.** Mix, C. L., Med. Clin. N. A. 9: 1255-1260. 1926.

The case described occurred in a woman 67 years old. Tachycardia was absent, nor was there any tangible thyroid enlargement. Exophthalmos, loss of 83 pounds in weight, and other typical symptoms of the disease were present, with a basal metabolic rate of plus 97 per cent.—I. B.

**Case of hyperthyroidism simulating primary heart disease.** Priest, W. S., Med. Clin. N. A. 9: 1337-1351. 1926.

The author calls attention to the importance of differentiating cases of thyroid hyperfunction without exophthalmos and without obvious goiter from those of primary heart disease. Basal metabolism determinations should be made in all cases of alleged heart disease not responding to treatment with a view to the discovery of possible thyroid toxicity.—I. B.

**Hyperthyroidism and its relation to benign tumors of the thyroid gland.** Reinhoff, W. F., South. M. J. 20: 901-906. 1927.

The thyroid is in a state of flux as shown by the histological changes brought about by feeding iodine in exophthalmic goiter. All patients with hyperthyroidism show histological changes. The term toxic adenoma is not justified, for the gross condition of the thyroid is the result of the balance between hypertrophy, hyperplasia, and involution, which may have taken place in the gland recently or over a long period.—J. C. D.

**Action of ergotomine on the blood in Basedow's disease and in animals** [Die Wirkung von Ergotamin (Stoll) beim basedow und in

tierversuch auf die Blutzusammensetzung]. Rothschild, F., and M. Jacobsohn, *Ztschr. f. kin. Med.* 105: 406-409. 1927.

Briefly the authors have shown that upon using 0.5 mgm. ergotamine-tartrate on patients with Basedow's disease, a vagus effect on the blood predominated; this expressed itself through a drop of blood sugar, cholesterin and calcium and rise of non-protein nitrogen and potassium. Organic and inorganic phosphorus fell as when adrenalin and thyroid extract are used. In animals, the sympathetic effect predominated: blood sugar, phosphorus and calcium rose, potassium and cholesterin fell, and non-protein nitrogen rose slightly.

—H. J. J.

**Mongolian maldevelopment, upon the basis of clinical, statistical and anatomical investigations (Beitrage zur Kenntnis der Mongoloiden Missbildung auf Grund klinischen, statistischen und anatomischen Untersuchungen).** Van de Scheer, W. M., *Abh. a. d. Neurol. Path. Psychol. und ihren Grenzgeb.* 41: 1-162. 1927.

Mongoloid form of idiocy belongs to the class of congenital malformations. The congenital anomaly can be carried back and attributed to a narrow amniotic sac, which exerts its influence during the sixth or seventh week of embryonic life. The disturbance in development of the amnion results from a faulty implantation of the ovum in an abnormal endometrium. On the basis of a local condition of the endometrium, the author advances the above hypothesis, especially since there is no evidence in the history of the parents, emotional states of the parents or any other factor which is responsible for the condition. In favor of it is the advanced age of the mother in many instances, the mongolian is the last born, history of still births and miscarriages and the absence of mental defects in other members of the family except perhaps the occurrence of another mongolian idiot.—M. B. G.

**Influence of the thyroid gland of selacians and teleosts on the metamorphosis of frog tadpoles [influence de la gland thyroïde des sélaciens (*Scyllium canicula* Cuv. et *Sc. stellare* Gthr.) et des téléostéens (*Cyprinus carpio* L.) sur la métamorphose des têtards des anoures (*Rana temporaria* L.)].** Sembrat, K., *Compt. rend. Soc. de biol.* 97: 1508-1510. 1927.

Transplants materially hastened metamorphosis.—J. C. D.

**Adolescent thyroid and goiter in Steiermark (Über Jugenschilddrüse und Kropf in Steiermark).** Orator, V., and E. Walchshoper, *Deutsche Ztschr. f. Chir.* 201: 310-319. 1927.

On the basis of operations and necropsy findings in Steiermark, where goiter is endemic, the authors report the following classifications: In early infancy the thyroid shows definite lobular markings,

the lobules being made up exclusively of solid colloid-free parenchyma (new-born type). From the fourth year on is found the central vesicle type with distinct lobar and lobular structure, but in the center of each lobule can be seen an empty vesicular structure surrounded by a solid colloid-free parenchyma. This type with the emptied vesicle is spoken of as the "open and transitional type" as long as the vesicle is empty, but if it becomes filled it is then known as the normal thyroid of childhood. The normal adolescent type found after the age of 16 years shows small follicles filled with colloid arranged in pronounced strata about a large central vesicle.

—M. B. G.

The fate and characteristics of mongolian children (Schicksale und charakteristik mongoloider Kinder). Steinen, R. v. d., *Monatschr. f. Kinderh.* 35: 495-504. 1927.

Of the 73 children whose follow-up history was obtainable, 46 had died, the majority of either lobar or broncho-pneumonia. Only 4.1 per cent reached the age of 20 years. Congenital heart conditions were present in 14 children and generally caused death before the end of the third year. Practically all of the children in the series showed a tendency to upper respiratory infections. None of the children were proficient in any occupation; the memory was fair, but all were deficient in arithmetic. They were able to perform manual work. Of those who survived, three-tenths showed some maldevelopment, while of those who died, eight-tenths.—M. B. G.

The relationship of endemic goiter to tuberculosis (Über den Endemischen Kropf und seine Beziehungen zum Tuberkulose). Salsani, O., *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* 40: 146-153. 1927.

Tuberculosis in the active form was found in all of the cases (48) of parenchymatous goitre seen at the out-patient department of the Vienna Surgical Clinic. The type was either of the inflammatory primary complex or of the proliferating primary complex. Iodosterine did not produce any favorable results. The author feels that this type of goiter has tuberculosis as its chief etiologic factor.

—M. B. G.

Indications for thyroidectomy. de Takats, G., *Illinois M. J.* 51: 306-307. 1927.

The author advises thyroidectomy in (a) large diffuse colloid goiters in individuals past 21 years of age in whom medical treatment has been of no avail, and in simple large adenoma with or without cystic degeneration; (b) goiters producing pressure symptoms, as well as all substernal goiters; (c) functional hypothyroid cases with adenoma and hyperthyroid cases in which the basal metabolic rate is above plus 15 per cent.—I. B.

# Endocrinology

## *The Bulletin of the* *Association for the Study of* **Internal Secretions**

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### STUDIES OF THE ENDOCRINE GLANDS\*

#### II. The Pituitary

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#### PART I

In a recent communication one of us (Rowe, 1) has presented the details of an objective method for the differential diagnosis of endocrine disorders, together with an analysis of a series of one thousand cases to which it has been applied. The present paper deals with the results obtained in the study, by this method, of a series of cases, four hundred in number, in which some form of pituitary malfunction was demonstrated as a primary etiological factor. As the full details of the method have been published in the earlier communication, it is enough here to state that a very thorough physical examination and the compilation of a detailed medical history are supplemented by a long series of laboratory tests, the significance of which

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\*Presented at the Annual Meeting of the Association for the Study of Internal Secretions, Atlantic City, N. J., May 26, 1925.

has been demonstrated by elaborate preliminary studies. In addition, detailed examinations by the specialists of the consulting staff give supplementary information concerning indications of endocrine disease, and, even more significantly, the presence or absence of disorders of a non-endocrine etiology. The inadequacy of a single observation to establish a diagnosis except in the rarest instances has already been stressed in the preceding paper. Individual objective facts gain diagnostic significance only as they are interpreted in the light of a large number of correlated observations and measurements. Facts elicited are interpreted in terms of endocrine malfunction only after every known non-endocrine cause has been eliminated by observation and test. This does not preclude the recognition of coexisting endocrine and non-endocrine disorders, but does prevent grave omissions on the one hand, and seriously misleading diagnoses on the other. In a shortly forthcoming paper on non-endocrine disorders, cases illustrative of this point will be presented. In one, the entire picture, save only the blood morphology, was typical of thyroid dysfunction. The case was one of leukaemia.

In presenting this material no attempt can be made at a survey of the literature. The compendious monographs of Cushing (2), Blair Bell (3), Engelbach and Tierney (4), Falta (5), Biedl (6) and others, together with the series of excellent articles in "Endocrinology and Metabolism" (7), give reviews which are as complete as the rapidly growing literature will permit. When to these earlier compilations are added the several hundred titles that yearly appear, the impossibility of adequate presentation is obvious. Reference will be made only to contributions, the details of which bear directly on the thesis in hand. Omission of recent papers implies no adverse opinion of their merit.

The present series of four hundred pituitary cases is selected from nearly two thousand patients referred for diagnosis. The presentation of so large a mass of data within reasonable compass offers manifest difficulties. The tabulation of averages offers the simplest solution, but here, in some measure, the means defeats the end. The algebraic summation of the results of opposing influences by its very nature destroys the magnitude and direction of deviations from the conventional normal which are of diagnostic significance. To illustrate: a judiciously

blended group of extreme thyrotoxicoses and myxedemas would exhibit a strictly normal average basal rate. Further, in any group of cases but a few will be of an advanced order, and the inclusion of many incipient cases betraying tendencies rather than an established condition will lessen the average magnitudes and hence the apparent significance of variation. On the other hand, with an adequate number of cases, because of these limiting conditions, variations of relatively small amount may assume a real significance.

An added complication arises, in the present instance, from the fact that the hypophysis consists of at least two, and possibly four, functional entities.

Waiving, in the interest of simplicity, the subtleties of dialectic, we shall designate as "hyperfunctional" those cases in which the observed facts equate with what is generally conceded to be the evidence of an over-activity. Equally, the "hypo-functional" group show a picture of relationships the opposite of the foregoing. The cases designated as "dysfunctional" are those in which the two lobes are demonstrably not at the same functional level, and includes those cases in which one or both lobes are undergoing functional involution.\* This group contains a wide variety of conditions determined by the relative functional variations in two bodies, each with three potential levels of activity and seemingly well differentiated as to independent influence on metabolism. As might well be predicted, a very large percentage of the cases here reported fall in this category.

Yet another element of confusion arises from the fact that different disease pictures are engendered by the relation of the time of development of the glandular malfunction to the age, and particularly to the sex status of the individual. These differences have been well recognized and so frequently described as to require no further elaboration here. That the intermediate or end results of a given pituitary aberration will be greatly influenced in certain directions by the maturity of the individual, is established, and in any scheme for the presentation of data, sufficient differentiation must be employed to take cognizance of significant variations.

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\*The shifting sugar tolerance during the progress of acromegaly, so clearly demonstrated first by Cushing and his associates (8), is a case in point.

Recognizing the limitations implicit in this method of presentation of data, it remains only so to order the arrangement as to reduce these obscuring conditions to a minimum. While the group contains few of the spectacular cases of extreme malfunction which have been reported from other sources, all of the earlier cases, the study of which laid the foundation of the present generalization, exhibited clear-cut and unmistakable lesions demonstrated by previous surgical intervention, radiography or subsequent necropsy. Well established acromegaly prior to the onset of the involutional changes, is usually unmistakable. But the same definition is lacking in the other syndromes which bear the names of Froehlich, Lorain-Levi, and others.

From the clinical standpoint there is a certain possibility of confusion in the hypofunctional states of several of the endocrine group, and only by objective methods of great completeness of detail can they be differentiated with any measure of certainty.

Turning to the results of the study, the various physical measurements have been collected in the following table. The highest and lowest values observed for each measurement are included as giving an idea of the range of variation in each of the several quantities. In conformity with the convention discussed above, hypofunctional states are designated as "—," the complementary hyperactivities as "+," while the several types of dysfunction are grouped under the caption " $\pm$ ." The summary values are, in many instances, unduly influenced by the relative numerical preponderance of the dysfunctional group. The use of unweighted averages, however, would only introduce a different disturbing element.

In discussing these data it must constantly be borne in mind that the magnitudes recorded are possibly influenced by wholly extraneous factors of which no cognizance may be taken. Such an element as the percentage distribution of different races presenting widely different characteristics,\* could well modify data obtained by two independent investigators. The

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\*In this connection, to ascribe racial peculiarities to varying levels of endocrine function, wholly ignoring the manifest influences of environment, nutrition, and climate, shows more enthusiasm than judgment. Further, these ethnic groups fail to show many of the bodily peculiarities that their alleged endocrine origin would presuppose.



seeming predominance of females over males in this series may be due to an inherent greater susceptibility on the part of the female, and equally could be referable to a greater frequency of recourse by that sex to medical aid. Our figures showing a greater incidence of the "hyper"-functional state in the male are not in accord with the far more comprehensive observations either of Sternberg (9) nor of Hinsdale (10). Our larger

TABLE I  
PHYSICAL MEASUREMENTS

Observation		Unit	Gland Function			Grand Average
			-	±	+	
Number of Cases		400	83	310	7	
Sex	Male	%	29	36	57	40
	Female	%	71	64	43	60
Age	High	years	71	70	63	
	Low	years	9	6	17	
	Average	years	32	33	42	33
Height	High	cm	195	189	172	
	Low	cm	130	103	155	
	Average	cm	165	164	166	164
Sitting Height	High	cm	100	99	91 5	
	Low	cm	69	56	85	
	Average	cm	87	87	88	87
Sitting Height Index			0 527	0 530	0 530	0 530
Chest Girth	High	cm	128	145	98	
	Low	cm	58	54 5	67	
	Average	cm	86	81	84	82
Weight	High	kgm	150 0	180 0	78 8	
	Low	kgm	21 6	15 7	54 9	
	Average	kgm	73 7	66 3	65 6	67 8
Area	Average	sq m	1 81	1 72	1 73	1 74
Lung Volume	High	c c	6200	5400	3600	
	Low	c c	1330	600	2380	
	Average	c c	3050	2900	3050	2930

series of hypo- and dys-functional cases accord with the frequently recorded observation of a greater incidence in the female. Whatever the cause, the fact remains that in this group the females predominate in ratio of 3 to 2. The small number of the true hyperpituitary group makes certain of the absolute magnitudes of somewhat less significance than with the other two divisions. The differences in relative physical proportions of the two sexes comes in as an obscuring factor in the absolute figures here recorded. Both the relation of Sitting to Total

Height (Sitting Height Index) and of the former to the chest girth (not here reported), are definitely different in the two sexes. Presentation on a sex basis would, however, multiply data without adding much to the significance of the picture.

Clarity of outline can be secured by relative figures, using two sets of standards for the sexes, and this has been done in the later tables wherever it is found to be informative. The only really salient sequence here traceable is in the greater tendency toward obesity with the lower activities, and even here the heaviest subject was a boy weighing 180.0 kgm., with a pituitary dysfunction of the type most common in our experience in which the anterior lobe is under-, the posterior, over-active.

The apparently greater age of the hyperfunctional group accords well with the general observation of the more frequent occurrence of this condition in adult years, and the frequent prepubertal appearance of glandular failure.

As was stated above, absolute values are influenced by several extraneous factors, to allow for which would entail a complexity that would obscure the issue. Certain correlations have been suggested which allow for sex and occupational differences by the establishment of graded standards. One set of such correlations have been suggested by Dreyer (11). As one of us (12) has shown, only the Dreyer comparisons based on Sitting Height (designated "Trunk" by the author) are significant, the other correlations leading to extrapolations of a most misleading character. Further, it is a better practice to use but one occupational standard for each sex, varying the limits of tolerance to accord with individual habit. We have adopted Dreyer's male "A" and female "B" standards as most nearly conforming to observed American conditions. West (13) has also established correlation between lung volume (designated "Vital Capacity" by Dreyer), area, and standing height. Our practice has been to report the average of the Dreyer value with the average of the two West comparisons. By so doing a weight factor (through the area) is introduced without leading to the absurd values of Dreyer's weight comparison. For the reason given above, only West's male and female standards are used. With both the West and Dreyer comparisons it has been found that the female standards accord better with male children than

do those of the adults of their own sex. The results of these comparisons are given in Table II.

TABLE II  
"VITAL CAPACITY" COMPARISONS

Observation		Unit	Gland Function			Grand Average
			-	±	+	
Weight .	High .	%	+123	+179	+28	65
	Low.	%	-23	-42	-11	
	+ Average.	%	+33	+27	+13	
	%	%	73	62	71	
	- Average.	%	-9	-13	-8	
	%	%	29	38	29	
	Net Average	%	+22	+12	+7	35
Chest	High	%	+52	+65	+16	66
	Low.	%	-15	-24	-13	
	+ Average	%	+14	+12	+7	
	%	%	76	63	71	
	- Average	%	-7	-7	-7	
	%	%	24	37	29	
	Net Average	%	+9	+5	+3	34
Lung Volume. .	High	%	+18	+20	-13	11
	Low	%	-56	-62	-31	
	+ Average.	%	+8	+6	-	
	%	%	19	10	0	
	- Average	%	-21	-22	-19	
	%	%	81	90	100	
	Net Average	%	-16	-19	-19	89

The values given above possess a certain definite significance. The tendency of the pituitary case to over-weight is clearly shown, as well as the influence of the level of functional activity on this manifestation. The correlations between chest and weight are excellent. While the girdle type of obesity that suggests pituitary malfunction should influence the chest less than the hip measurement, increase in girth of the former may confidently be predicted.

The depression of observed over calculated lung volume is definite, and again might well be anticipated. Peabody (14) has shown the depressing influence of cardiac disease and of general weakness, and other writers have made similar observations (15). The significance here is in the relatively slight diminution (slightly less than one-fifth) of the predicted capacity. Further, the value is probably in excess of the truth, as the general obesity in this condition makes the West normal standards somewhat high. No correction is made for this, however, as the results thus obtained are better suited for the dem-

onstration of diagnostic differences in cases as actually met in practice.

The end results of certain phases of metabolism can best be evaluated by analysis of the urine, and certain of the observations permitting of tabular presentation are collected in Table III.

TABLE III  
URINE MEASUREMENTS

Observation		Unit	Gland Function			Grand Average
			-	±	+	
Volume.	High	c.c.	5800	3680	2000	1190
	Low.	c.c.	330	350	860	
	Average	c.c.	1360	1150	1280	
Spec Grav.	High		1.036	1.039	1.028	1.019
	Low.		1.005	1.007	1.012	
	Average		1.018	1.019	1.019	
Albumin.		%	19	25	57	24
Casts		%	11	18	43	17
Sugar		%	0	25	71	
'Urobilinogen'.		%	21	29	71	29
Amylase Index	Average		19	18	20	18
Salol	Average	min.	72	70	81	71
Urea Curve	Normal	%	54	50	0	49
	Delayed	%	14	11	33	12
	Progressive.	%	5	7	0	6
	Low.	%	27	32	67	33
Phenol Sulphone 2-hour Elim.	Phthalein, Average	%	52	51	55	51

While the dissociation of diabetes insipidus from pituitary disease, suggested, among others, by Houssay (16), and more recently by Bourquin (17), as deriving from injury to the mammillary bodies, eliminates this condition in some measure from a priori inclusion in the hypophyseal group, it does not preclude the frequent observation of a pituitary polyuria. The contiguity of the controlling bodies to the endocrine gland implies frequent damage to them secondary to hyperplasia of the pituitary.

Elimination here is seen to be fairly normal in spite of an appreciable number of cases of lowered kidney permeability demonstrated by the other observations. The sequential relationship of the appearance of albumin and casts is well illustrated in the percentages of the three groups. Even more strik-

ingly does the incidence of glycosuria as an evidence of posterior lobe over-function manifest itself. This finding has been very frequently recorded, although many of the observers, even the more recent, persist in regarding the condition as a diabetes engendered by pituitary influence on the pancreas. The untenability of this position is soon to be discussed at length elsewhere.\*

A striking and significant finding in this group of cases is the positive response of the urine to para-dimethylamino benzaldehyde, the "urobilinogen" test of Ehrlich. That this response depends upon the presence of urobilinogen, is hardly probable. Positive tests have been demonstrated by many in a variety of liver conditions, and one of us (1) has shown it in primary anaemia. Like so many color reactions in which an organic complex is the reagent, the test lacks in specificity and may well be given by a series of substances which need have only a single organic group in common. Its appearance in cases of pituitary disease is of a definite diagnostic import when the non-endocrine causes have been experimentally ruled out. The Salol test, of no great significance, approaches normality. Designed as a rough test of gastric motility, it is primarily dependent on kidney permeability. The provocative urea curves agree in substance with the urine analyses in implying a lowered level of kidney activity, and the Phthalein test offers such measure of confirmation as may be derived from any test subject to so many extraneous disturbing influences.

Summarized, it may be said that a disturbed kidney function seems to be concomitant to pituitary malfunction—probably by indirection through general metabolic disturbance,—that posterior lobe over-function frequently produces a glycosuria which is not diabetic, and that a positive response to para-dimethylamino benzaldehyde is shown by nearly one-third of the cases in this series.

It has been the practice of this laboratory to make nitrogen partition examinations on all urines analyzed. This serves the two-fold purpose of estimating the nutritional level of the patient,† and of indicating metabolic disturbance in abnormality

\*Rowe, "Non-Diabetic Glycosurias." In preparation.

†For example, the obese patient who acknowledges a food intake of a glass or two of milk in the twenty-four hours, and whose 24-hour urine contains 25 grams of nitrogen. Equally valuable is the recognition of a partial protein starvation with its far reaching effects.

of the partition formula. As has been pointed out by one of us (18), it is not necessary to carry out an elaborate nitrogen metabolism experiment for these data to assume significance. The relative amounts of the several constituents in health depend, as was first shown by Folin (19), on the total nitrogen elimination, the endogenous and exogenous moieties of the several factors determining relative losses with lowered protein intake. The data from the nitrogen partitions are given in Table IV.

TABLE IV  
NITROGEN PARTITION

Observation	Unit	Gland Function			Grand Average
		—	±	+	
Total Nitrogen..... Av...	gms.	9.37	9.28	10.98	9.33
Urea Nitrogen..... Av...	%	79.9	80.3	77.8	80.2
Uric Acid Nitrogen..... Av...	%	2.2	2.1	1.6	2.1
Ammonia Nitrogen..... Av...	%	4.3	3.7	4.8	3.8
Creatinin Nitrogen..... Av...	%	4.6	4.5	4.4	4.5
Residual Nitrogen ..... Av...	%	9.0	9.4	11.4	9.4
% of Cases = or > 9%.....	%	39	54	71	51

The nitrogen averages show a general level of protein utilization well above Sherman's (20) maintenance level. It is true that they do not indicate a "luxury" consumption, but it should be borne in mind that the majority were hospital patients.

[For reasons that have never been fully explained, the average person during a hospital residence drops to a lower nutritional level for protein than his usual habit elsewhere. This is not due to any change in the dietary *per se*; it is our routine practice to give the patient not less than 1.5 grams of protein per kgm. body weight.\* With the average weight as a basis, this would correspond to an elimination of some fifteen grams of nitrogen—making allowance for the fraction not absorbed. The actual output is but 60 per cent of the predicted. The phenomenon has been observed by every worker in this field, but so far as we know no attempt at an explanation of it has appeared.]

As the result of a long series of observations, partial report of which has already appeared (18), the residual or undetermined nitrogen partition has been assigned a value of 9 per cent

\*Needless to say, in cases like that of our eleven-year-old boy weighing nearly four hundred pounds, this schedule fell far short of realization.

as the upper limit of normality. Folin (19) found values less than 8 per cent when the nitrogen output was reduced to less than four grams, but as the quantity is obtained by difference and incorporates all the analytical errors for the determined constituents, the higher value is felt to be more representative.

All of the groups show a level indicative of disturbed metabolism, and this is more marked in the hyper-active group, both in amount and in frequency of occurrence. If the hypo-active condition represented the terminal phase of a cyclic change—as is certainly partially the case in acromegaly—this might well be expected, the body re-establishing a new metabolic equilibrium at a lower level with the subsidence of the abnormal activities. This will not account for all cases but raises an interesting point for speculation in regard to a certain proportion of them. Another interesting feature is the relative and absolute increase in the uric acid elimination in the hypofunctional group. Falta and Nowaczynski (21) have noted an increase in uric acid output in acromegaly, but found a lowered elimination in a single case of head trauma which they diagnosed as “*dystrophia adiposo-genitalis*” from a tumor in the region of the hypophysis. In this latter instance the question may well be raised if this single patient may be regarded as typical of true pituitary disease. In the study on the residual nitrogen already cited, it has been shown that while the high values are due in part to increase in the amounts of substances normally present in very low concentration, there yet remain significant amounts of nitrogen which cannot be allocated to any known constituent. The nature of this residuum is now under investigation.

As the blood is the forerunner of the urine, the results of the routine examinations of fasting blood may next be considered.

In the main it will be seen that the blood chemistry bears out the implication of the urine findings as to the functional capacity of the kidney. The most striking feature is the high value for uric acid, and more particularly the large percentage of cases showing a high uric acid with normal levels for the other nitrogenous constituents. Some years ago Hammett and his associates (22) observed an increase in blood uric acid in four out of six experimental subjects to whom desiccated pitu-

itary extract was administered per os. The present results leave no doubt that a high blood uric acid, independent of the other nitrogenous elements of the blood and not deriving from nephritis or gout, is found in disease of the pituitary. The diagnostic significance of this fact is important.

TABLE V  
BLOOD CHEMISTRY (AND SEROLOGY)

Observation		Unit	Gland Function			Grand Average
			-	=	+	
Non-Protein Nitrogen	Av.	mgm.	32	33	36	33
% > 35 mgm		%	22	25	57	
Urea Nitrogen.	Av.	mgm	15	16	17	16
% > 17 mgm		%	12	16	29	
Uric Acid	Av	mgm.	3 6	3 8	3 8	3 8
Net* % = or > 4 mgm.		%	21	33	20	31
Creatinin	Av.	mgm.	1 5	1 5	1 6	1 5
Residual Nitrogen	Av.	mgm	15 2	15 1	17 1	15 1
Sugar	Av.	mgm	97	95	93	95
% > 120 mgm		%	1	1	0	1
% < 80 mgm		%	1	5	0	4
+Wassermann		%	0	0	0	0
+Kahn (presumptive)		number	0	0	0	0
+Spinal Fluid		number	0	?	0	?
+Schwartz-McNeil		number	0	1	0	1

An interesting result is the normal blood sugar observed and, particularly, that the hyperfunctional group present the lowest average. In a single case which we have had under continuous observation for over four years, and which is to be described in detail elsewhere as well as noticed in this paper, we have recorded high blood sugar levels. These were the result, however, not of the pituitary tumor per se, but possibly to injury to the brain produced during treatment or the coexistence of a true diabetes. The details on this case (S-326, B-269, B-475) will be given briefly later in this paper. It will be noted that one case in the series is reported with a questionably positive spinal fluid examination. There was an earlier history of lues, seemingly properly treated, the single doubtful test together with a number of findings indicating a pituitary dysfunc-

\*All demonstrated cases of nephritis and gout have been deleted



tion. Incidentally, the case has cleared up on anterior lobe medication. Under the circumstances there seemed to be no impropriety in including this case in the series.

The data for the Blood Morphology are given in the next table.

TABLE VI  
BLOOD MORPHOLOGY

Observation		Unit	Gland Function			Grand Average
			-	±	+	
Haemoglobin.	Av.	%	88	88	94	88
Erythrocytes.	Av	10 <sup>6</sup>	4 94	5 01	5 36	5 00
Color Index..	Av.		0 89	0 88	0 88	0 88
Leucocytes.	Av	10 <sup>3</sup>	7 9	7 8	8 5	7 8
P. M. N. Neutrophiles. .	Av.	%	56	57	64	57
% = or > 75%.		%	0	5	29	
Lymphocytes.	Av.	%	35	36	27	36
% = or > 33%.		%	53	62	43	59
Eosinophiles. .	Av	%	2	3	1	3
Net % = or > 3%*		%	28	31	14	30
Monocytes.	Av	%	7	4	8	4

The general picture is one of normality. The tendency toward a secondary anaemia reported by others (23), (24), (25), (5) has not been observed by us. In fact, the highest values are found in the frank hyperactive cases. Falta (5, p. 274) would seem to regard the reduction as characteristic of the later stages. Later (p. 312) in connection with hypophyseal dystrophy, he observes only a lowering of haemoglobin. Even this deviation does not appear in the present series. Isolated cases, naturally, exhibit some secondary anaemia. Our lowest haemoglobin was 50 per cent and the averages as given above are normal. A slight relative lymphocytosis finds expression in the average value, while nearly two-thirds of the individual subjects show lymphocytes above the conventional normal number. Falta (5, p. 312) makes the same observation on a small number of cases. Our observation has been that where the slightest increase in these cells is not observed, there is apt to be a marked decrease

\* Cases in which a non-endocrine cause of eosinophilia was demonstrated have been deleted

with values for the neutrophiles exceeding the normal. The lymphoid bloods, in our experience, are found with all the endocrine states—and in an appreciable number of non-endocrine conditions.

The other point of significance in the pituitary blood picture is the slight upward tendency of the eosinophiles. This fact has been reported by a number of observers (24), (5, p. 274, 312), (2), (26), and in single cases the observed percentage has assumed most significant proportions. Failure to eliminate non-pituitary causes, at least in the earlier cases, may account for some of these latter. Nearly one-third of the patients show this tendency even after all those demonstrating non-endocrine causes of eosinophilia have been deleted. The combination of an eosinophilia of moderate degree coupled with an increase in the uric acid of the blood, the other constituents exhibiting normal levels, is seemingly peculiar to pituitary disturbances. Such observations play an important part in establishing the general picture, all parts of which are necessary for definite diagnosis.

A most important chapter in the study of endocrine disorder, deals with the respiratory metabolism. The data of our observations together with certain other informative concomitant measurements are collected in Table VII.

While the significance of the respiratory metabolism in endocrine disorders has been stressed by many writers, the striking variations produced by aberrant thyroid activity has tended to minimize consideration of the other ductless glands. This is seemingly particularly true as regards pituitary disease, and in the paucity of the published data is found one reason for the conflicting opinions which even today come to expression. Another and even more potent influence tending toward disharmony lies in the classification of pituitary conditions. While acromegaly is initially the result of a state of hyperfunction, the gland certainly may undergo functional involution, and in many cases in the later stages presents a laboratory picture which is the antithesis of that of the initial phase. As far back as 1912, Cushing (2, p. 22) emphasized this point and criticized adversely the findings of earlier investigators who had ignored this most significant observation. The designation of cases as

acromegalic without further qualification inevitably leads to confusion. Falta's analyses of the few cases of Magnus Levy (27), of Salomon (28), and of Bernstein and himself (5, p. 276) leads to the conclusion that uncomplicated acromegaly does not increase the basal metabolism, confirming the opinion of his quoted authorities. Confusion of the glycosuria of this condition with diabetes, and the assumption that the latter greatly increases metabolism, is one factor leading to his erroneous conclusions.

TABLE VII  
RESPIRATORY METABOLISM

Observation	Unit	Gland Function			Grand Average
		-	±	+	
Basal Metabolism Deviation					
High ..	%	-4	+33	+23	+33
Low ..	%	-24	-28*	+14	-24‡
+ Average ..	%	-	+8	+18	
% ..	%	0	8	100	
- Average. ..	%	-15	-13	-	
% ..	%	100	92	0	
% > + 10% ..	%	0	2	100	
% between +10% and -9% ..	%	19	34	0	
% = or < -10% ..	%	81	64	0	
Blood Pressure					
Systolic Av. ..	mm	117	113	165	
% < 110 mm ..	%	27	39	0	
Diastolic Av. ..	mm	72	73	95	
% < 65 mm ..	%	26	23	14	
Pulse Rate. Av. ..	per min	72	72	83	72
% = or < 70 per min ..	%	43	43	14	
Respiration Rate Av. ..	per min	14	15	14	15
% = or < 10 per min. ..	%	11	9	0	
Temperature Av. ..	deg F	98 4	98 0	98 3	98 1
Alveolar CO <sub>2</sub> Av. ..	mm	40	39	38	
% > 35 mm ..	%	57	67	71	66
% = or < 30 mm ..	%	5	3	0	3

The slight rise in basal rate observed by Benedict and Joslin (29) in diabetics without emaciation and confirmed by the latter's more extended observations (Joslin, 30), is usually more than compensated by the low nutritional level incident to the condition. This was originally pointed out by Lusk (31), and since confirmed by numerous other observations (32). Benedict and Homan's (33) hypophysectomized dog showed a definite decrease. Snell, Ford, and Rowntree's (34) observa-

\*Complicated by partial inanition  
‡Uncomplicated See Note 1.

tions are scarcely pertinent, as of their seven cases five were of diabetes insipidus, a condition not certainly directly referable to pituitary disorder. Means (35) found a lowered rate in obesity of pituitary origin, an opinion more recently confirmed by others. Boothby and Sandiford (36) analyze thirty cases of acromegaly showing respectively 50 per cent over  $+10$  per cent, 43.4 per cent with the conventional normal range of  $+10$  to  $-10$ , and 6.6 per cent below the latter figure. These values equate perfectly with the varying functional level of glandular activity incident to the disease. Less easy to explain are the same authors' report on fifty-eight cases of "hypopituitarism" in which with 53.5 per cent below  $-10$  per cent and 34.5 per cent in the normal range, they report 6.8 per cent (4 cases) with rates above  $+16$  per cent. The warrant for including these latter under the diagnostic caption, is questionable. In the light of the experience of this laboratory they would seem far more probably dysfunctional types in which the anterior lobe still manifested some measure of over-activity. We have had opportunity to study several patients (a typical case protocol is included in the later discussion) over an extended period during which, as the result of their own decision, they remained without treatment. In these, the slow involution of glandular activity has been directly apprehensible, and the terminal phase, a true hypopituitary state with lowered basal rate and greatly increased sugar tolerance. Boothby (37) concludes, however, that "there is very little evidence that the secretion of any part of the pituitary gland . . . acts as a calorigenic agent." A number of other papers might be cited, but they would serve only to add to the contradictory opinions contained in the representative articles discussed above. Analysis of all existing data, irrespective of opinion, would seem to show that an over-activity of the anterior lobe conditions a moderate rise in the basal rate, and that the complementary failure produces an equivalent depression. There is an interesting suggestion of correlation in the facts that the anterior lobe is that portion of the gland essential to life, and that the great majority of cases of pituitary disease presenting well marked symptoms, show a lowered activity of this portion. Even in acromegaly, when the hyper-active phase obtains long enough to produce the striking structural changes characteristic of the syndrome, there is a defi-

nite tendency toward a recession of activity to an ultimate hypofunctional end state.

Before turning to the data of the present report it may not be inappropriate to re-emphasize one point. The diagnoses here presented are not the result of a single measurement apparently confirming a series of subjective evidences suggestive of some classic syndrome. They are, on the contrary, based upon a long series of carefully executed tests, the significance of each of which has been thoroughly defined by preliminary studies both with normal controls and cases whose surgical history defined the underlying pathology. These concrete facts were taken as the basis for the interpretation of the equally carefully acquired results of the physical examination and the subjective elements of the medical history. Finally, no one bit of evidence was accepted as indicating endocrine malfunction until every non-endocrine potential cause of such fact had been ruled out by test and observation. Finally the patients have been submitted to the therapeutic test of the indicated medication with observed improvement in clinical condition and laboratory findings. It may seem that undue emphasis is laid on this aspect of the work, but the record of diagnostic contradictions which were a genetic factor of this whole study makes us feel that this consideration is of basic and fundamental importance.

In the table given above it will be observed that the extremes of variation in the uncomplicated cases fall between  $-24$  per cent and  $+33$  per cent. The prevailing downward tendency is shown by the dominant fraction exhibiting values below  $-10$  per cent. In the earlier stage of over-activity there is an unmistakable increase in the basal rate which, as the figures in the present series show, has never exceeded a moderate amount. In the small group of purely hyper-active cases, all adults, there were evidences of acromegaly in every patient. The downward tendency of the blood pressure, as was noted by Cushing in his series, is clearly manifest. Individual cases may fall below a systolic reading of 100, but the tendency is toward a moderate decrease falling short of the levels seen with the other endocrine glands. The seeming hypertension of the over-active cases is probably not due to the well known pressor action. Several of the cases in this group had a complicating cardio-renal

condition and, while a specific influence is not definitely ruled out, conservatism would reject it. The fall in blood pressure recorded in the course of acromegaly does not necessarily presuppose an initial hypertension. The average pulse rates are normal—in the hyper-functional group, a little raised—but in the two large groups nearly one-half were below 70. Inspection of a series of cases shows a definite tendency downward, but rarely does the rate assume the low level of the thyroid failure. The respiration rate is seemingly not affected by this nor, in fact, by any of the endocrine glands except the thyroid. A rapid rate can usually be referred to some exciting cause other than the gland function. Body temperature shows normal averages with but moderate departures in the individual cases. Alveolar carbon dioxide shows equally normal tensions. Two-thirds of these cases are above the conventional low normal limit, and only three present a level suggestive of an existing acidosis. To summarize then, the level of functional activity of the anterior lobe produces like deviations of moderate degree in the basal rate. The blood pressure and pulse manifest a downward tendency—exception has already been noted in the pure hyper-functional states—while the remaining observations conform substantially to the generally accepted normal values.

As the respiratory exchange is seemingly controlled by the anterior lobe, so the carbohydrate metabolism is generally regarded as reflecting the functional level of the posterior lobe of the gland. The data for this observation are found in Table VIII.

Before discussing the table, a few points may be explained. First, galactose is the sugar used, for reasons discussed in full elsewhere (38a, b, c, d, e), and the tolerance is determined by the appearance of sugar in the urine, it having been shown by one of us (38b) that the relationship of the dose to this level determines the shape of the so-called diagnostic curve. Further, while the male gonad has no influence on the galactose tolerance, with the female the opposite is the case. Normal tolerance ranges from the twenty grams of the prepubertal girl, through the forty of the adult woman to a post-menopausal level between thirty and forty. Pregnancy produces a lowering, first to thirty and ultimately to the prepubertal level of twenty, returning gradually to the original normal level after delivery. For this

reason, the expression of the tolerance dose in grams is misleading, and percentage variations from the individual's normal must be substituted. For the sake of uniformity, a like convention is adopted with the data of the male group.

TABLE VIII  
GALACTOSE TOLERANCE

Observation		Unit	Gland Function			Grand Average
			-	±	+	
Male						
Dose	High	gms	70	60	20	
	Low	gms	40	5	5	
% above Normal		%	100	5	0	
Average Deviation of Dose		%	+73	+67	-	+70*
% equal Normal		%	0	13	0	
% below Normal		%	0	82	100	
Average Deviation of Dose		%	-	-50	-53	-52*
Female						
Dose	High	gms	120	80	20	
	Low	gms	30	5	10	
% above Normal		%	100	5	0	
Average Deviation of Dose		%	+74	+80	-	+77*
% equal Normal		%	0	2	0	
% below Normal		%	0	93	100	
Average Deviation of Dose		%	-	-53	-67	-63*
Summary						
% above Normal		%	100	5	0	
% equal Normal		%	0	6	0	
% below Normal		%	0	89	100	
Average + Deviation*		%	+74	+74	-	+74*
Average - Deviation*		%	-	-52	-60	-56*

A cursory inspection of the table demonstrates that the pituitary exercises a profound influence on the capacity of the organism to utilize carbohydrate. Examination of the dysfunctional group demonstrates further that the posterior lobe exhibits a tendency toward over-activity as marked as is that of the anterior toward under-activity. The numerical predominance of this group is certainly not fortuitous, as these cases are drawn from a group of nearly two thousand patients submitted for diagnostic study. That the superior limits should exceed the inferior, is to be expected from the numerical relationships. In fact, it is somewhat surprising that they show so

\* Not weighted for relative number of cases

close an agreement. The magnitudes speak for themselves and require no discussion. Obviously, the tolerance for galactose offers a valuable diagnostic point.

With the general differential picture of the three types of malfunction portrayed with certain inherent limitations in the preceding tables, the consideration of certain other pertinent matters not susceptible to tabular analysis may next claim attention.

## PART II

In spite of the important advances that have been made in our knowledge of the pituitary gland during the past ten years, there is still much ignorance in regard to it, and especially in regard to the effect of disturbances in its function as contrasted with the results of tumor growth involving the organ upon bodily nutrition and metabolism. Due largely to the work of Cushing (39) and his collaborators much more is known concerning "surgical" pituitary disorders than those not demanding operative intervention.

This lack in regard to functional disturbances is due largely to the fact that, acromegaly excepted, there has been no certain method of establishing the diagnosis of disturbed pituitary function in any individual patient save by surgery or autopsy, and a painstaking analysis of cases in which the diagnosis was in many instances uncertain has not appealed to those to whom abundant material was available.

This paper comprises an analysis of clinical and laboratory findings in a series of patients in whom the diagnosis of pituitary malfunction seems reasonably established by clinical symptoms, laboratory findings, and the progress of the condition while under observation. The laboratory data are based on an analysis of 400 cases; the clinical findings embrace only one hundred.

There are several reasons for choosing this smaller number of cases for clinical analysis. First, all the patients in this smaller series have come under the immediate observation of one of us (C. H. L.) so that there has been a fair chance properly



to evaluate the symptoms and signs presented; second, the number seems sufficiently large to permit reliable conclusions; and third, it is the same as the number of acromegalics and patients with pituitary tumors recently reported by Davidoff (40) and Frazier and Grant (41), respectively.

In contradistinction to their patients all of those comprising the clinical section of this paper had hypofunctional disturbances of the pituitary, that is, either hypofunction of both lobes, or that condition described by Cushing (39), in which the anterior lobe is underactive while the posterior lobe is either normal or overactive. Inasmuch as it is impossible to distinguish between these conditions clinically, they are all grouped together in this analysis.

#### CLINICAL FINDINGS

In tabulating our clinical findings an attempt has been made to follow the plan used by Davidoff (40) in order that a comparison of findings might be easily made. Such a comparison brings to light very important points of difference and similarity between the two groups.

#### *Incidence*

Functional disturbance of the pituitary other than that caused by tumor of the gland is considered by the majority of physicians to be a rare condition, and important more as an interesting curiosity than as the cause of important disturbances of body function. This was our own point of view at the beginning of this study, but as our method of diagnosis has become more reliable, we have found that the pituitary is no more immune to disturbances of function than is the thyroid or the pancreas—its humbler position in medical thought is due not to its relatively infrequent involvement, but to the fact that this often exists unrecognized. In a series of 1000 cases examined in our clinic, 65 per cent have been found to have definite and significant disturbances of metabolism of endocrine origin. Of these, 12 per cent have presented symptoms and laboratory findings diagnostic of thyroid hypofunction; 14 per cent of ovarian dysfunction; 1.3 per cent of Addison's disease; while 28.4 per cent have been classed as disturbed pituitary function.

On the basis of these figures we are forced to the conclusion that disturbance of pituitary function is more common than is generally appreciated, but that the cause of symptoms produced by early or moderate disturbances is not generally recognized. Unless the patient exhibits definite acromegaly, gigantism, or marked obesity of the pituitary type, the possible connection of hypophyseal function with the syndrome is usually not even considered. Yet Davidoff states that "the surgically verified cases also show that hypophyseal adenomas *without* acromegaly are about five times as frequent as those *with* acromegaly." If adenomata of the pituitary gland produce their most characteristic symptom only once in six times, it is not illogical to believe that disturbances in its function may often be present without giving rise to so-called pathognomonic symptoms, which allow a tentative and tenuous diagnosis to be made by inspection. Our conclusion concerning the incidence of disturbed pituitary function in so far is supported by proven facts.

*Race.* All the patients in this service were members of the white race, as were Davidoff's. Beyond this our analysis does not go, as the birthplace of the patients was not recorded, and in these days of wholesale immigration it is impossible to determine the nationality of a patient by the character of his patronymic. Our impression is that the majority were born in America, and that of those whose names were diagnostic the largest number of patients of foreign extraction were Jewish. This may be due to the population from which the majority of our patients come, or to a real susceptibility of the Jewish race to endocrine instability.

*Sex.* In our series there were 68 females and 32 males. At first sight this does not seem to agree with the findings of other observers (42) (43) who find acromegaly, at least, equally distributed between the two sexes. In Eidelsberg's (44) series of cases of hypopituitarism, however, the distribution was 55 per cent females and 45 per cent males. Reference to our larger series shows a predominance of males in the hyperfunctional, a preponderance of females in ratio of 2 to 1 in the dysfunctional and nearly 3 to 1 in the hypofunctional groups. The preponderance of females in our series is doubtless due in some part to the fact that men find it more difficult to take time for

hospitalization, so long as their illness is not incapacitating. Another factor may exist in the type of the disorder.

*Age.* The age of the patients at the time they entered the clinic is given in the following table:

TABLE IX

Age in years	Number of patients
1-10	2%
10-20	30%
20-30	22%
30-40	17%
40-50	20%
50-60	8%
60-70	1%

The extremely low figure for the first decade is undoubtedly unreliable. Metabolic studies on young children require special apparatus and special cooperation on the part of the patient. Undoubtedly the figure would be higher were we able to study satisfactorily all the children under ten years of age who present themselves at the hospital. It is significant, however, that between ten and twenty years are noted the greatest number of patients. Undoubtedly this is due to the fact that puberty occurs in this decade. In talking with these patients one is impressed with the large number who connect the beginning of their complaint with puberty, and the undoubted increase in endocrine activity during that epoch is an important factor in activating a potential functional weakness of the pituitary. The importance of its integrity for normal sexual development is well known, and our figures serve only to accentuate the fact that puberty is an important factor in changing a potential pituitary failure into an overt form. The sudden drop in incidence in the sixth decade also suggests the intimate association of the pituitary and sex functions.

An attempt to determine accurately the age of onset of symptoms in our series was unsuccessful, because of their gradual nature and the tendency of patients to connect their complaints with some manifestly unimportant event. Puberty, or its absence long after it should have occurred, was the most common single datum obtained.

The next largest group, all women, dated the beginning of their complaints from the birth of their first baby, irrespective

of their own age, while a somewhat smaller number presented themselves because of sterility. It is manifestly impossible to determine the duration of complete sterility unless one concludes that it existed from birth, or earlier. The significant fact is the large number of patients in whom pituitary malfunction is connected in some way with demands for increased activity due to some phase of the sexual life.

*Occupation.* No important relationship between occupation and pituitary disturbance could be detected.

#### FAMILY HISTORY

In only one case was there a definite history of acromegaly in a near relative. In ten cases there were one or more instances of abnormal height in near relatives. In eight cases there was a story of family obesity similar in distribution to the patient's. Nine patients gave apparently reliable stories of diabetes in near relatives. In three per cent, thyroid disorders appeared in the history of the immediate family, and in seven per cent there was the statement that some near relative had had "gland trouble." The significance of this last statement is open to question, but exclusive of that number, and of those with a family history of obesity, there is a history of definite endocrine disorder in some near relative in twenty-three per cent of our patients. As in diabetes (45) and thyroid disorder [see Janney (7)] there is evidence that the integrity of pituitary function is subject to inheritable factors.

#### MARITAL HISTORY

Only fifty-five per cent of our patients were married. This figure is much lower than Davidoff's. If, however, we exclude those below twenty years from our calculation, the figure will be raised to eighty per cent, which is not significantly different from his. We are inclined to agree with him that this small number of marriages is due in considerable degree, to the blighting effect of pituitary malfunction on gonadal activity and sex life.

Of the productive marriages, the resulting number of children was one in 28 per cent, two in 23 per cent, three in 31 per cent, and four, five, and six in 6 per cent each. In this

group of patients who were not sterile the pituitary disturbance, so far as could be determined, did not antedate the pregnancies.

To summarize, only 55 per cent of our patients were married, 36 per cent of those married were sterile, and an additional 28 per cent had less than the normal average number of children, convincing evidence of the importance of disturbances of pituitary function in influencing fertility. Were we certain of the potency of the patient's mate in each marriage and of the relation of beginning of symptoms to the date of marriage in every case, the figures would be still more significant. A study of sterility is now being carried on in our clinic which we hope will contribute important information on this question.

#### PAST HISTORY

*Development.* Eighty patients gave histories of normal physical and mental development. This coincides nearly with Davidoff's figure for acromegals (40). In 13 per cent there was a history of significant early obesity or abnormal skeletal growth. Seven per cent had had difficulty in keeping up with children of their age in school. None of these figures is particularly significant, and the criteria are unsatisfactory. No conclusions can fairly be drawn from them. Much more significant are the findings in regard to puberty. Of 92 patients beyond normal puberal age, delayed or absent sexual development was present in 32, almost 35 per cent. Of these, two were males, thirty were females, although of the entire group thirty were males and sixty-two females. In other words, nearly 50 per cent of the female patients and only 6 per cent of the male patients beyond the normal puberal age showed delayed sexual development. It is, of course, far easier to determine accurately the onset of maturity in the female than in the male, and it is probable that the apparent low percentage of delayed sexual development in males is to some degree explained by the lack of a definite symptom. It would hardly account, however, for the entire difference in the figures. Here is a question which demands further investigation.

The answer may lie in the greater susceptibility of females to endocrine disturbances in general, and it is possible that this susceptibility is due to the fluctuating endocrine balance asso-

ciated with menstruation and pregnancy. The apparent demonstration by Frank (46) of the appearance and disappearance of a female sex hormone in the circulating blood is of possible significance in this connection.

### *Previous Illnesses*

The incidence of previous illnesses in our series of patients is shown in the following table:

TABLE X

## PAST HISTORY

Operations . . . . .	57%	{ 40%—removal of tonsils and adenoids 8%—appendectomy. 9%—miscellaneous.
Trauma . . . . .	7%	{ 2%—involving head. 5%—other parts.
Scarlet Fever. . . . .	19%	
Typhoid. . . . .	7%	
Pneumonia . . . . .	7%	
Influenza . . . . .	19%	
Tonsillitis . . . . .	58%	
Meningitis . . . . .	5%	
Mumps . . . . .	37%	
Miscellaneous . . . . .	12%	{ 3%—rheumatic fever 3%—sinusitis. 3%—tuberculosis. 3%—malaria.
Relation to Present Illness . . . . .		{ Definite 1%—pregnancy. Possible 4%—infections. Not established—95%.

Two significant facts appear in this table: one, that the onset of the condition is so gradual that only 5 per cent of patients can connect it in any way with preceding illness; the other, that there is an extremely large percentage of definite focal infection in these patients. Even discounting the present enthusiasm for removing tonsils, the fact that 40 per cent of our patients had had tonsillectomy cannot be easily dismissed. Appendectomy is an operation concerning which there is little hesitation at present, yet the table shows only one appendectomy for each five tonsillectomies. The incidence of tonsils so diseased as to demand removal must, therefore, be accepted as significant.

In this connection, the figures for tonsillitis are confirmatory and significant. Only patients who had had frequent and repeated attacks of "sore throat" are included in the 58 per cent charged with tonsillitis, yet the incidence is significantly greater than that of mumps, a common disease of childhood, easy of identification. The conclusion may fairly be drawn therefore that tonsillar infection and disturbed pituitary function coexist in a significantly large number of cases.

The question as to which condition causes the other is as yet not definitely answered, but observation of our patients after removal of diseased tonsils strongly suggests that focal infection is in many associated with the depression of the glandular activity. The following case is significant.

#### PROTOCOL 1

The patient was a tall, thin school girl, 17 years of age, presenting amenorrhea as her chief complaint. The menses had never been established and she had always been below her predicted weight. During the past year she had grown very rapidly.

The family history is without significance, except for a paternal aunt who did not menstruate until after her sixteenth birthday.

The patient's past history records only a few minor ailments in childhood and a mild attack of influenza in 1920. But for her present difficulties, the general level of her health has been excellent.

*Physical Examination:* The patient was a tall, very thin, moderately nervous girl, intelligent and co-operative; with a height of 67 inches in her shoes and a weight of 92½ pounds in her underwear. The skin and mucous membranes were somewhat pallid. The teeth showed evidence of much dentistry. The tonsils were large and scarred and the pillars injected. She had infantile breasts; there was neither pubic nor axillary hair, and examination by the rectum showed an almost infantile uterus. The pulse was slightly high and the blood pressure definitely low.

*Laboratory Examination:* The urine was practically normal, except for a very slight trace of albumin. The blood showed 75 per cent haemoglobin, normal erythrocyte count, a slight leukopenia and a substantially normal leucocytic formula. The smear showed a moderate achromia. Blood chemistry showed a low non-protein and urea nitrogen and high uric acid. a blood sugar value of 120, a value probably above the truth. The basal rate was reported as identical with prediction. This value was undoubtedly high.

*Comment:* The delayed menarche, absence of breast development, and body hair, the small uterus and the patient's body configuration are typical of hypophyseal infantilism. Pelvic examination under anæsthetic confirmed the findings by rectum, and eliminated other pelvic disorder.

*Treatment and Progress:* The patient was given pituitary extract, anterior lobe, beginning with 8 grains daily and rapidly increasing to 16 grains. Tonsillectomy was advised but refused.

On January 15, 1925, her weight was 108¼ pounds; hemoglobin, 90 per cent; blood pressure, 100-70. The breasts had developed a

little and there was a slight growth of axillary and pubic hair. A week ago she had severe cramps in the pelvis, lasting 8 hours, the breasts being sensitive at that time.

On June 10, 1925, her weight was 113½ pounds. She had not menstruated, but the breasts were now normal in size and the pubic and axillary hair normal in amount.

On December 3, 1925, her weight was 115 pounds. Her general health was excellent, with no menstruation or molimina.

June 24, 1926. Four days ago menstruation began and persists. She was feeling well. Her weight had increased to 119½ pounds. Her height was 69½ inches. The basal metabolic rate was  $-4$  and the pulse rate 72.

July 15, 1926. The gynaecologist reports that the uterus is much larger, being practically normal in size.

January, 1927. The patient reports having had one short period, and one attack of pelvic cramps lasting 12 hours.

Tonsillectomy was performed in March, 1927.

June, 1927. The patient reports another menstrual period, of normal character. She complains of frequent frontal and vertical headaches, beginning about four weeks ago. At the same time, there is occasional mild vertigo. She is advised to diminish the dose of pituitary extract to 10 grains daily.

December, 1927. Menstruation has continued regularly since June. The headache disappeared when medication was diminished. She reports herself in perfect health.

*Comment:* The interesting features in this case are: First, the response to oral pituitary medication; and, second, the effect of removing focal infection. The idea that pituitary extract is not effective when given by mouth is, we believe, unjustified. Undoubtedly, the dosage usually employed is insufficient, and in certain patients even large doses produce no typical results. Focal infection is a probable factor in many cases showing negative results. Conditions within the digestive tract possibly interfere with absorption in others. The possibility of success is, however, great enough to justify treatment by oral medication, provided one is prepared to push the dosage if necessary, and to remove any inhibiting factors which exist in the individual patient. The whole question of endocrine medication will be considered at length in a series of papers now in preparation.

The permanent establishment of menstruation following removal of the tonsils, together with the simultaneous appearance of headache relieved by diminishing the dose of pituitary extract can only be interpreted as indicating an improvement in pituitary function when the focal infection was eliminated. It is our belief that focal infection, especially of the tonsils, is a definite etiological factor in pituitary hypofunction. No other significant relationship appears in the table.

#### THE EXISTING CONDITION

One can hardly use the term "disease" in relation to departures from health due to disturbed function without definite organic change. The majority of our patients were able to "carry on" in spite of their handicaps, but their lack of health



was sufficient seriously to interfere with their efficiency and enjoyment. The symptoms and signs as recorded in the clinical histories, are tabulated below.

TABLE XI

Symptoms and signs as recorded in clinical histories:

<i>Symptom</i>	<i>Incidence</i>
Enlargement of acral parts.....	6%*
Enlargement of sella turcica on x-ray examination...	5%
Disturbance of menstruation.....	51%†
Headache .....	34%
Complete amenorrhoea .....	8%‡
Visual disturbances.....	7%
Excessive perspiration.....	3%
Hypertrichosis .....	28%
Drowsiness and lethargy.....	8%
Changes in weight (greater than $\pm 10\%$ ).....	73%
Diminished libido .....	11%
Asthenia .....	36%
Low blood pressure (less than 120 mm. Hg.).....	28%
Paraesthesias .....	20%
Polyphagia .....	4%
Polydipsia .....	1%
Constipation .....	29%
Vomiting (with present illness).....	10%
Rhinorrhoea .....	1%
Photophobia .....	1%
Uncinate attacks.....	3%
Failing memory.....	1%
Decrease of body hair.....	0%
Persistent lactation.....	1%
Failure of breasts to develop.....	1%
Epistaxis .....	0%
Choked discs .....	3%
Vertigo .....	14%
Tinnitus .....	17%
Deafness .....	15%

\*Definite acromegaly.

†Of females over 14 years of age.

‡Of females over 14 years of age.

A comparison of the above findings with Davidoff's table of symptoms (40) shows certain interesting similarities and differences. Those symptoms which are in all probability due to disturbed nutrition show a strikingly similar incidence in both tables; those due to enlargement of the sella, present in large numbers in his table, are rare in ours.

Enlargement of aeral parts appears, at first sight, to be an exception to this rule. Davidoff, however, studied only patients having such enlargement, while our study comprises all types of disturbed pituitary function. Moreover, we have excluded from our table many patients in whom disturbances of aeral growth, or asymmetry of development was definitely present although there was not the facial distortion characteristic of acromegaly. If we were to include in our table all those patients who showed asymmetrical skeletal growth, the figure would be greatly increased. From the diagnostic point of view, bodily asymmetry is one of the most important stigmata of disturbed pituitary function, past or present.

Distortion of the sella demonstrable by x-ray was absent in all but 5 per cent of our patients. This is, of course, no evidence concerning the function of the pituitary. Disturbance of its function may exist without affecting the sella outline and an abnormal sella shadow does not prove that the pituitary is in any way involved. This fact has been emphasized by Camp (47) and is well illustrated by the following case.

#### PROTOCOL 2

The patient was an English woman, 44 years of age, who was referred because of severe headaches. During the past twenty years these have occurred at fortnightly intervals. The pain starts suddenly, is severe and throbbing, and usually begins in the frontal or temporal region, later extending to the vertex. The pain lasts from one to three days and ends spontaneously and abruptly. During its course nothing affords relief. There are no associated disturbances, neither nausea, vertigo nor visual aberration. Eight years ago drainage of one maxillary antrum was performed in the hope of affording some relief. Following this, there was freedom from pain for about six months. At that time the patient had an attack of influenza, subsequent to which the headaches returned and have persisted to the present, gradually increasing in frequency and severity.

*Family History.* The father died of pneumonia at the age of 36; the mother of arteriosclerosis at 64. Four sisters and one brother are living; one sister has died of cancer. All members of the family are abnormally tall.

*Past History.* The patient reports several minor ailments and scarlet fever in childhood. She was undersized until 16 years of age, and then grew rapidly for the next two years, attaining her present height of 5 feet 7 inches. She had rheumatic fever at 18, and influenza as above noted. The catamenia was established at 16 and has apparently been perfectly normal.

*Physical Examination* shows a tall, somewhat emaciated white woman with prominent lower jaw. Beyond infected tonsils the findings were normal.

*Laboratory Examination.* The general 'uriné' picture was normal, except for one specimen showing a trace of albumin. The blood showed a slight relative lymphocytosis, but was otherwise not significant. The blood analysis gave low normal values for all the nitrogenous constituents, with a normal blood sugar. The basal metabolic rate was —4 per cent. The patient was 20 per cent under weight. The blood pressure shows a mild degree of hypertension. The sugar tolerance is normal, as are the eye findings. Radiography of the skull showed a large deep sella (Plate 1), and a slight thickening of the membranes lining the maxillary sinuses. On the basis of the appearance of the sella a diagnosis of slow growing pituitary tumor had previously been offered.

*Comment.* Although the x-ray findings suggested a pituitary tumor, the patient's general condition and more definitely the normal laboratory examination and eye findings failed to support such a diagnosis. The x-ray also disclosed infected sinuses, and these were operated upon successfully, but a mastoiditis developed as a sequel. Since her recovery from this latter condition she has had no more severe headaches, the condition being confined to a rare mild attack of brief duration.

*Note.* If a diagnosis of pituitary tumor on the radiographic findings of the sella is ever justifiable, the picture presented in this patient would seem to be an ample warrant. The laboratory examination, however, was wholly negative, and, more significantly, the result of treatment would seem to indicate a purely non-endocrine cause of the patient's difficulty. We do not feel that a single observation of this type ever forms a firm basis for a diagnosis, and that the carefully compiled history and physical examination, supplemented by complete metabolic studies cannot be supplanted by any single observation.

In a study of pituitary function, radiography of the sella turcica is valuable because it helps to establish the presence or absence of tumor, not because it affords any information concerning functional disturbance.

Of much greater importance, we believe, is the evidence gained by a complete study of the eye grounds and visual fields. This was done, in our patients, by Dr. W. D. Rowland, to whom our thanks are due for his most important contribution to this study. His findings in 84 cases are tabulated in Table XII

The importance of studies of the eye in pituitary disturbance has been emphasized in a recent article by Frazier and Grant (41). We have found it of enormous value both in estab-

lishing the diagnosis of pituitary disturbance, and in separating the cases in which tumor is present from those in which there is no growth. Even in the latter group contraction of the visual

TABLE XII

## EYE FINDINGS IN EIGHTY-FOUR CASES

Choked Discs.....	3%
Yellow Discs .....	19%
Hazy Discs .....	10%
Optic Atrophy .....	1%
Vessels Sclerosed .....	3%
Contracted Visual Fields.....	29%
Enlarged Blind Spots.....	64%

fields is not uncommon, and definite enlargement of the blind spots is the rule rather than the exception. The character of the contraction of the visual fields frequently leaves little doubt that they are due to the pituitary condition, especially as sinus disease has been ruled out in our patients. Whether the blind spot enlargement is due to pressure from a pituitary which is slightly enlarged or to nutritional changes is not so certain, but from the point of view of diagnosis this finding is extremely important. The lack of subjective visual disturbances is no evidence that the visual fields are normal for we have seen a considerable number of patients with markedly contracted fields who stated that there was no difficulty with the vision. That such contractions may be caused by simple hyperplasia or functional disturbance of the pituitary is evident from the work of Finlay (48), Erdheim and Stumme (49) and Carvill (50).

*Disturbances of the Menstrual Cycle.* Fifty-nine per cent of our female patients showed disturbance of menstruation, if we consider those adults in whom menstruation was entirely absent with those in whom it was present but abnormal. In four of our patients with amenorrhoea, menstruation had never appeared, and examination showed juvenile pelvic organs. In four others, menstruation had been established for varying periods and the pelvic organs were not demonstrably abnormal.

The disturbance of the menstrual cycle in our series was characterized by late menarch, short duration of catamenia and scantiness of flow, increased intermenstrual interval, and ab-

PLATE 1



Case B 412 X ray of sella showing probable tumor Patient gave no evidence of functional pituitary disease

sence of significant pain. These changes in menstrual behavior are, we believe, characteristic of an associated pituitary hypofunction as contrasted with other endocrine disturbances. Menstruation may be markedly disturbed by abnormal thyroid function, but in that condition menorrhagia and shortened intervals are as common as the reverse, while in ovarian hypofunction pain is commonly a prominent symptom. The group of disturbances mentioned above, especially if found in a patient with asymmetrical physical development demand a careful study of the functional level of the pituitary.

*Weight Disturbances.* In this series 73 per cent (65 per cent in the larger series) of the patients showed a variation from normal weight, as calculated by the West and Dreyer Standards, of more than 10 per cent. This difference is not necessarily pathological, but forms a fair basis for classification. Of those whose weight was not normal, 57 per cent were overweight. Underweight was found chiefly in adolescents showing the Levi-Lorain type of disturbance, and seldom amounted to more than —20 per cent, the maximum deficiency recorded being —30 per cent. Overweight while by no means limited to adults, was more common among those over twenty, and was of more marked degree. As a rule overweights of 40 per cent were not uncommon, and the maximum in this group was 60 per cent. The obesity showed almost without exception a predilection for the middle third of the body, the neck, wrists, and ankles remaining nearly normal. Characteristically, these patients gain weight very rapidly, and under certain conditions lose it rapidly, only to regain it again. The obesity is stubbornly resistant to dietary treatment, it being usually impossible to reduce weight and keep the patient well at the same time. It seems logical to suppose that the obesity is connected with the disturbed carbohydrate metabolism of these patients, and from a practical point of view, rigid curtailment of carbohydrate intake is more effective than general reduction of calories in combating this type of obesity.

Besides the definite tendency to abnormal weight, our patients showed clearly the effect of pituitary activity on skeletal growth by the number above "normal height." Of those who had passed the growth period, 25 per cent of the males were

over 6 feet, and 18 per cent of the females were over 5½ feet in height. The definite upper limit of normal height is difficult to fix, and these figures are given merely to make clear the definite tendency to increased height in these patients. Not only was their height above the average, but in the majority there was a history of very rapid growth during a limited period of time, most often coincident with or shortly after puberty. Such rapid growth, as well as the abnormal height, must mean a glandular hyperactivity at the time of their occurrence, and we believe that in many of our patients this hyperactivity preceded the state of hypofunction which existed when they were studied. Certainly neither symptom furnishes any valuable evidence concerning the state of pituitary function when the patient comes for examination—they merely suggest that at some time there has been a hyperactivity of the gland. This may still be present, or function may have returned to normal, or have swung still further into the hypoactive phase.

*The Skin.* The most frequent cutaneous abnormality encountered in our series was hypertrichosis, which was definitely present in 28 per cent, mostly women. Abnormal loss of hair was not present in any of our patients, if we except absence of body hair in the cases of delayed puberty. The changes in the hair consist in altered quality and distribution. The hair of the head, axillae and pubis is thick, oily, and vigorous, and there is a marked tendency toward increased hairiness of the trunk and limbs, most striking in women, in whom hair is usually not found in those sites.

Other than the hypertrichosis, 23 per cent of our patients are described as having some cutaneous abnormality such as roughness, dryness, or excessive oiliness. Cold skin, so common in hypothyroidism, was not noted. Neither were definite eczemas, which are also common in hypothyroidism. Vasomotor instability, frequently encountered in patients with depressed ovarian function, was conspicuous by its absence.

The teeth which might be expected to participate in disturbance of nutrition affecting the hair and skin, were described in definitely abnormal in 28 per cent of our patients. The variations from normal were rapid and general decalcification, malposition, or delayed eruption. The two latter conditions were

always associated with other signs of delayed development, while decalcification was present in the obese patients with increased tolerance for sugar. The exact relation of carbohydrate and calcium metabolism is not known, but our findings bear out the idea held by many dentists, that the teeth of individuals who consume large amounts of sugar are usually soft.

*The Thyroid Gland.* Twenty-three per cent of our patients showed symmetrical, elastic enlargement of the thyroid gland. All of them had basal metabolic rates below normal. For a complete discussion of thyroid enlargement in pituitary disease the reader is referred to the recent paper of Cushing and Davidoff (51). As yet the interrelation of the two conditions is not understood, and a discussion of theories must be omitted here. The important fact from our point of view is that thyroid enlargement and low basal metabolic rate do not always mean hypothyroidism, and do not, therefore, always demand treatment with thyroid extract.

*The Tonsils.* Attention has already been directed to the seemingly important role played by tonsillar disease in pituitary malfunction, as judged from the clinical histories. The physical findings in our series lend confirmation to the idea already expressed, for in only 25 per cent of the patients were normal tonsils present. Forty per cent had had their tonsils removed, and in an additional thirty-three per cent the tonsils, in the examiner's opinion, were definitely infected. The criteria for this judgment were the presence of injection of the tonsillar pillars, with large or irregular tonsils from which pus could be expressed. Tonsils which were merely large or irregular, without injection of the pillars and yielding no pus on pressure, were not termed infected.

*The Heart.* Neither in the histories of the patients, the physical examinations, nor the electrocardiograms were there any evidence of organic heart disease in this group of patients. This is extremely interesting because of the high incidence of the tonsillar infection, the cause of so much organic disease of the heart. Moreover, in sharp contrast to derangement of the thyroid function, in which functional cardiac disturbances are so common, symptoms of such conditions were conspicuous by their



absence. Tachycardia was not noted in the series. Only two patients complained of palpitation, slight in amount and not caused by exercise. Bradycardia was rarely encountered, even in the patients with low basal metabolic rates. This is an interesting and important point, since in thyroid failure the pulse rate usually follows the metabolic rate downward. The fact that it does not do so in pituitary failure suggests that the bradycardia in hypothyroidism is not due solely to the low metabolism, and furnishes evidence of some importance in the clinical differentiation of the two conditions.

*The Blood Pressure.* Hypotension was much less marked in this series than in hypothyroidism. As a rule the pressures were within or near normal limits under ordinary conditions. Those tabulated in the first section of the paper were taken under basal conditions.

*Other Viscera.* Only two patients in our series showed evidence of pulmonary involvement. One had a thickened pleura following pneumonia, the other had tuberculosis. No evidence of disease of the abdominal viscera was found in the entire series.

*Neurological Findings.* Headache was the most common neurological symptom in the group, being present in 34 per cent of the patients with more than occasional frequency. It was usually described as frontal or vertical. So-called "migraine" was not common, in contrast to the findings in thyroid failure. Of the 34 patients with headache 25, or 73 per cent, showed yellow or hazy discs and enlarged blind spots, and 32 per cent contracted visual fields, but no papilledema or other evidences of increased intracranial pressure. This close association of headache and eye changes indicate that both are due to a common cause. In the absence of papilledema or contracted visual fields pressure by the pituitary can be eliminated as a factor and the most probable explanation lies in the disturbances of nutrition, characteristic of pituitary malfunction, and their effect upon nerve tissue in general.

That the entire nervous system shows evidence of disturbed function in conditions of abnormal pituitary function is shown by the work of Cushing (2), Davidoff (40), and others, and by the further neurological findings in our series.

*Parasthesias.* Twenty per cent of our patients complained of numbness and tingling of the extremities—symptoms common to other diseases in which nutrition is disturbed, i. e., diabetes mellitus, and pernicious anaemia. Ten per cent showed definite sluggishness of one or more reflexes, one case showed ataxia, and one, with thyroid enlargement, exhibited a fine tremor of the hands. All these disturbances are apparently the result of imperfect nutrition of the nervous system, as no other explanation fits the facts so well.

*Deafness.* Deafness has not been emphasized in connection with pituitary disturbances, but 15 per cent of our patients had definite hearing loss, as determined by the audiometer. In 5 per cent, catarrhal conditions could not be eliminated as a possible cause for the deafness, but in the remaining 10 per cent no catarrhal condition could be demonstrated, and the history was typical of the progressive non-catarrhal type—so-called otosclerosis. In the light of the known relation of that disease to pregnancy, and of our knowledge of pituitary function during and after pregnancy, the question arises as to whether otosclerosis is anything more than a nutritional disturbance of the auditory apparatus, brought about by metabolic changes, for some, though by no means all, of which the pituitary may be responsible. Work on this problem is going on in our clinic at the present time and seems to offer hope of the solution of a part, at least, of this baffling problem.

*Treatment.* It is generally believed that pituitary substance, administered by mouth, is inert. In our experience, this is not entirely true. In ordinary doses, no effect could be demonstrated in the majority of our patients, but doses of from one to two grams (15-30 grains) produced demonstrable results in a large number of individuals. The recent work of Menninger (52), demonstrating that in certain individuals epinephrine is effective given orally, reopens the whole question as to the effectiveness of endocrine preparations thus administered. It may be that variations in the gastric secretion of individual patients account for the variations in the effect of the preparation administered (53). Work is now being undertaken in our clinic to clear up this point, and the results of treatment will be discussed more fully in a later paper.

PART III

CASE PROTOCOLS

The cases have been grouped according to characteristic symptoms. Typical laboratory data are assembled in tabular form to conserve space.

TABLE XIII

Observation		Blindness		Deafness	
		Number B-70	Number B-71	Number B-130	Number B-238
Diagnosis	Anterior Posterior. .	— +	— +	— +	— +
Sex		Female	Female	Male	Female
Age . . .	(yrs.)..	25	49	53	29
Height ..	(cm.)....	159	153	178	155
Weight....	(kgm.). .	37 5	63 7	62 3	48 0
Weight ..	Dev. (%).	-30	+29	-10	+8
Lung Volume. .	Dev. (%).	-28	-26	± 0	-25
Basal Metabolism .	Dev. (%).	-25	-12	-24	-18
Pulse. . .	(per min.)..	64	72	52	70
Blood Pressure	(mm.).	116/80	154/84	102/68	112/66
Temperature	(deg. F.).	98 4	98 0	97 8	98 2
Alveolar CO <sub>2</sub> .	(mm.).	41	41	45	40
Urine Volume	(c.c.).	1980	870	910	1370
Spec. Grav.		1 008	1 025	1 028	1 010
Albumin..		+	0	0	+
Casts...		+	0	+	0
Sugar		0	0	+	0
Total Nitrogen	(gms.).	4 62	20 88	12 22	5 16
Residual Nitrogen	(%).	3 1	13 1	3 6	9 2
"Urobilinogen"		0	0	+	0
Phen. Sulph. Phth	(%). .	47	61	63	89
Gal. Toler., Deviation.	.. (%).	-75	-50	-33	-50
Non-Protein Nitrogen	(mgm.).	35	38	47	32
Uric Acid....	(mgm.)	6 3	5 5	4 5	4 1
Sugar. . . .	(mgm.)	76	84	83	87
Haemoglobin.	(%).	80	90	95	80
Erythrocytes.	(10 <sup>3</sup> ) .	4 21	5 51	5 95	4 22
Leucocytes.	(10 <sup>3</sup> )..	5 95	7 20	6 05	6 15
Lymphocytes. .	(%)...	45	35	40	45
Eosinophiles .	(%).	5	4	2	1

BLINDNESS

CASE B-70. The patient's chief complaints were partial blindness (chiefly in the left eye), headache, amenorrhea, and mental depression. Four years ago she began to have headaches, which gradually have increased in severity and frequency, and a few months before her admission necessitated suspension of work and later admission to a hospital. The eye condition came on gradually, but during the recent period of examination there have been intense pain, photophobia, and marked further loss of vision. The mental phase has been intermittent throughout the four years and has intensified with

the present illness. The patient matured at 16; the catamenia was regular and scanty up to four years ago. The periods then became irregular with increasing interval, and ceased entirely four months ago.

*Family History:* Both parents died of pulmonary tuberculosis, and one sister has recently recovered from it. A brother died at seven of meningitis and hydrocephalus.

*Past History:* Several minor ailments and diphtheria in childhood were recorded. She had influenza four years ago. There is a history of some deafness, pain in ears and tinnitus. The use of glasses earlier gave slight relief to the headaches. She has hacking cough, with expectoration. She has always had some nausea, followed during past few months by occasional vomiting.

*Physical Examination* shows an under-developed, poorly nourished white female of 25. The left eye is practically blind and with some nystagmus. The lungs show dullness in the apices and fine rales.

*Laboratory Summary:* The patient is much under weight and her lung capacity is diminished. The basal metabolic rate is —25 per cent; the urine volume is ample, with albumin and casts both present. Protein intake is inadequate for maintenance; residual nitrogen is normal. The galactose tolerance is 75 per cent below prediction. The blood uric acid is very high, with normal non-protein nitrogen. She has a slight secondary anaemia, lymphocytosis (45 per cent) and eosinophilia (5 per cent).

*Neurological Examination* shows positive Romberg, normal gait, inco-ordination of upper extremities; lesion of second pair and possible eighth nerve involvement.

*Eyes:* The left pupil does not react to light or accommodation. The right fundus shows papilledema (1 mm.); the left, small, superficial hemorrhage on the nasal side of the disc; the discs are yellowish. The right form fields are normal, the color field contracted; on the left, only a small upper nasal field remains (see plates). The right blind spot is somewhat enlarged; the left could not be delineated. The findings indicate an intercranial growth and lesion in left optic nerve at or in front of the chiasm.

*X-Ray:* The sella appears to be normal. Infiltration with calcification of the left lung are evidenced.

*Ears:* No abnormalities are detected. The Barany test gave normal results.

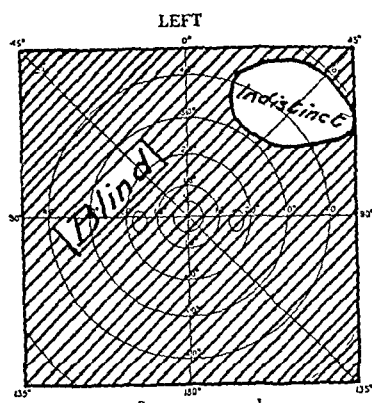
A *diagnosis* of pituitary dysfunction, with anterior lobe under- and posterior lobe over-active, coupled with pulmonary tuberculosis, was established. Because of the latter condition, operation was deemed inadvisable and anterior lobe *medication* was administered in the hope that normalizing the hypo-active portion of the gland might influence favorably the over-active fraction.

*Outcome:* The patient showed steady improvement and nine months later the eye findings were substantially normal (see plates) with 10/10 vision in the right and 10/12 in the left eye.

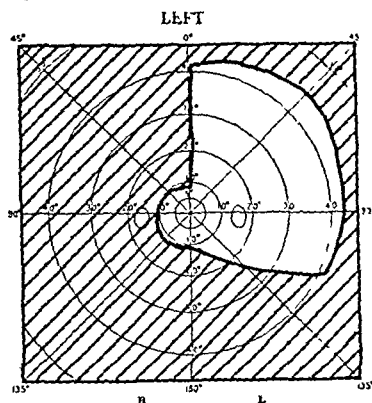
She was discharged to undergo treatment for the tuberculous condition. Three years later she reported with the pulmonary condition arrested. The eye examination showed nothing abnormal ex-

PLATE 2

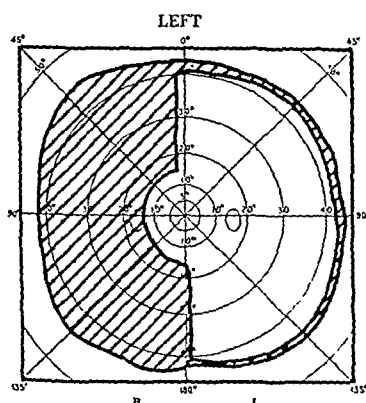
Case B-70. Pituitary blindness.



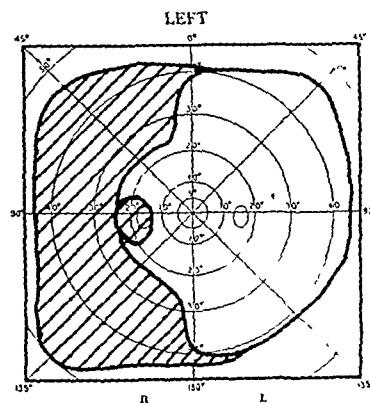
No. 1. July 31, 1923.



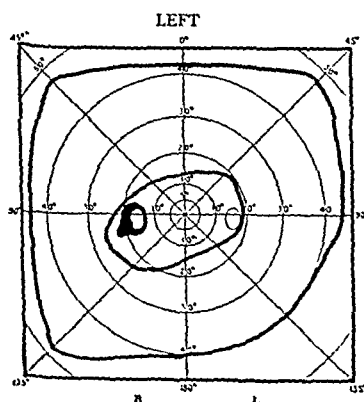
No. 2. Sept. 8, 1923.



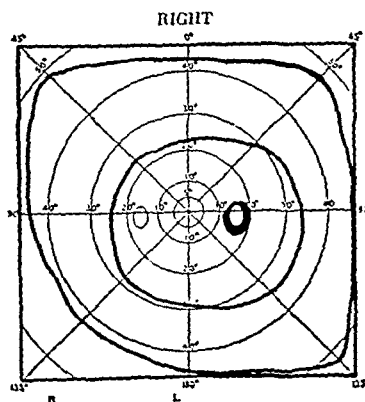
No. 3. Dec. 13, 1923.



No. 4. Feb. 20, 1924.



No. 5. May 3, 1924.



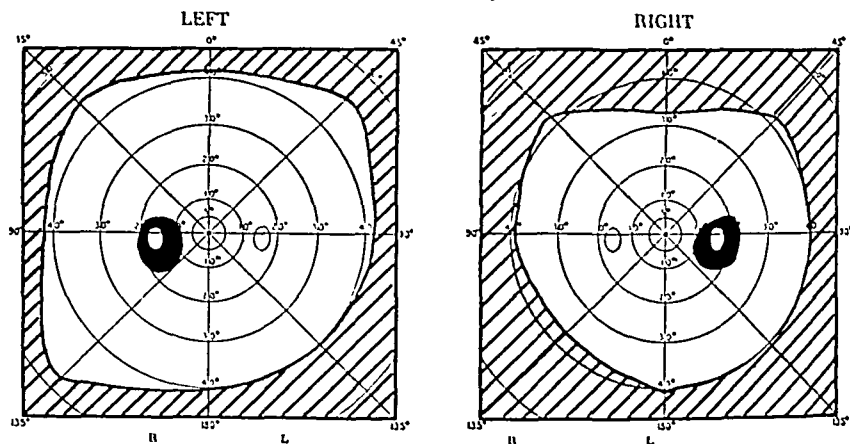
cept for persistence of the yellow discs. Her sugar tolerance had become 50 per cent above the normal, indicating a functional involution of the posterior lobe to a terminal under-active state. The patient also reported a partial resumption of the menstrual function.

**CASE B-71.** The patient's chief complaint was of a progressive blindness which had been first apprehended some seven months before. A diagnosis of neuro-paralytic keratitis had been made and treatment instituted, but without success.

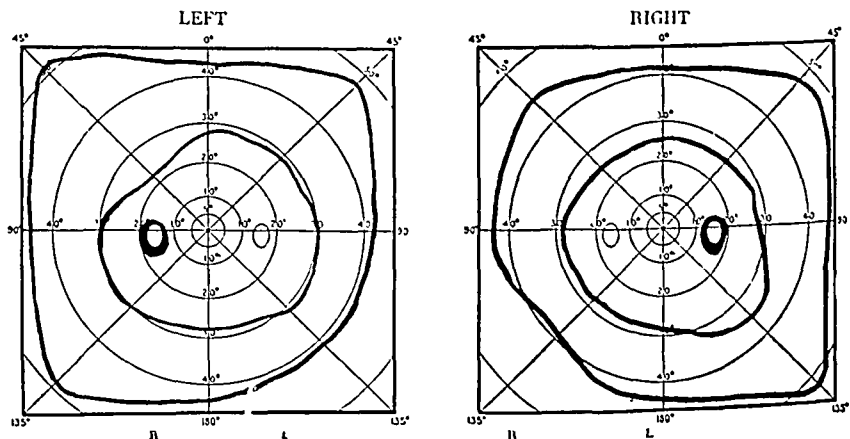
*Family History:* Four siblings were living and well. The father died of "growth in throat"; the mother, of old age.

### PLATE 3

Case B-71. Pituitary blindness.



No. 1. Dec. 5, 1923.



No. 2. April 23, 1924.

*Past History:* In addition to the usual minor ailments, the patient reports scarlet fever in childhood, an appendectomy at 36, and recently the extraction of a number of teeth. She had been subject to headaches in recent years and some emotional instability. Men-

struation began at 13; the periods were regular, every 28 days, with no pain, and normal amount. Her last period was eight months earlier; she is in the menopause.

*Physical Examination* shows a well developed, short, white woman of 49. She is somewhat obese, with a tendency to girdle distribution. The general physical examination disclosed no other abnormalities.

*Laboratory Summary:* The patient was 29 per cent over weight, with slightly low basal rate (the value recorded being probably somewhat high). She showed ample protein intake, with a high residual fraction of the urine nitrogen; sugar tolerance depressed; significantly high blood uric acid; a slight relative lymphocytosis and 4 per cent eosinophilia.

*X-Ray:* Shows some obscuration of the left antrum, increased density of the pituitary and erosion of the posterior clinoid process; also a retained root of the left first upper bicuspid.

*Eye Examination* showed marked impairment of vision; cornea and vitreous humour in both eyes somewhat hazy; yellow discs; blind spots enlarged; right form field contracted, left slightly so.

*Diagnosis:* Pituitary dysfunction, anterior lobe under-, posterior lobe over-active.

This case was also one in which operation offered, but doubtful hope of benefit for serious risk. Medication with anterior lobe pituitary substance was instituted with definite improvement in vision, as can be shown by the accompanying figures.

TABLE XIII-a  
DISTANT VISION RECORDS

Date	Right	Left
September 9, 1923.....	20/500	20/150
December 5.....	20/1000	20/150
January 2, 1924.....	20/200	20/80
February 27.....	20/150	20/40
April 23.....	20/80	20/40

The fields became practically normal and there was distinct reduction in the size of the blind spots (see plates).

The improvement here noted was probably due, in part at least, to an improvement in metabolism resulting from the glandular correction. In the supervening years there has been some loss of acuity, but the progress has been slow and the present status much superior to that at the initial contact.

## DEAFNESS

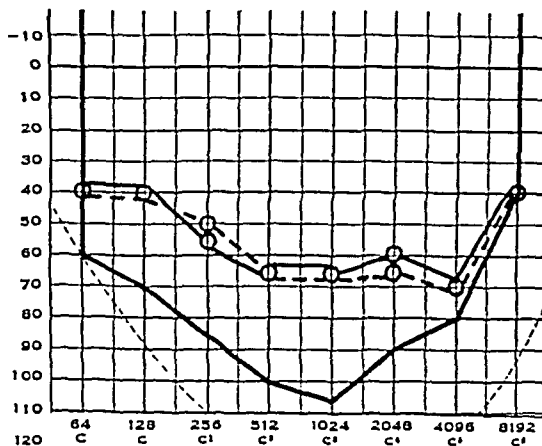
CASE B-238. The patient's complaint is of a bilateral loss of hearing. Eight years ago she had several severe sore-throats, to correct which a tonsillectomy was performed. The deafness, which was remarked just prior to the operation, has been progressive to the present.

*Family History* was not significant, except for two maternal uncles, who were both deaf following abscessed ears in childhood, and a brother who is also somewhat hard of hearing.

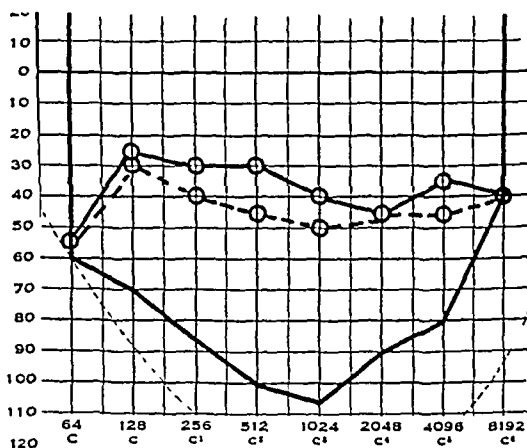
*Past History:* The patient had the usual children's diseases; an appendectomy one year ago; a laparotomy three years ago for unknown cause. She has had several breast abscesses. She has been married six years, has had no children, but three miscarriages, the most recent being eight months ago and following a long automobile ride. The catamenia began at 16; the periods have been irregular and have not resumed since her last miscarriage. There have been attacks of vertigo during the past six months, but no headaches. She has lost forty pounds in past few years, having dieted rigorously for obesity.

## PLATE 4

Case B-238. Pituitary disease with deafness (otosclerosis).



No. 1. Dec. 30, 1924.



No. 2. Aug. 5, 1925.

*Physical Examination* showed a well developed and nourished white woman of 49. Beyond a partial nasal obstruction and her deafness the examination disclosed no abnormalities.

*Laboratory Summary:* With a sitting height index of 0.51, the patient is 8 per cent above her predicted weight. This indicates that



at the height of her obesity (v. s.) she was nearly 50 per cent overweight. The basal metabolic rate is low; the blood pressure somewhat below normal. The urine shows albumin; its composition indicates a low protein intake; the residual nitrogen is slightly high. Her sugar tolerance is but half the normal. The blood uric acid is high. There is a slight secondary anæmia and the blood is lymphoid in type.

*Eye Examination* shows yellow discs, enlarged blind spots, some temporal cutting of the right form field, and some contraction of both color fields.

*Neurological Examination* affords no evidence of organic disease. It defines a social problem which seemingly does not contribute to the present condition.

*X-rays* of skull, sella, heart and lungs show no abnormalities.

*Barany* is normal.

*Pelvic examination* shows normal structures.

*Ear examination* showed no organic defect.

*Audiogram* (see plate) demonstrated a marked loss of hearing.

*Diagnosis and Outcome:* On the basis of the general picture, reinforced by the eye findings, a diagnosis of pituitary dysfunction with the anterior lobe under- and posterior over-active was established, and anterior lobe medication begun. The deafness gradually improved, as is shown in the audiogram (see plate) taken eight months later.

**CASE B-130:** The patient's chief complaint was of deafness, first noted some eight years ago and progressive since that time, though no great change has been noted in the past two years. Forty years before he had had a discharging ear, which soon cleared up and did not seem to affect the hearing. At the onset of the present condition there had been much tinnitus, but less in the past few years.

*Family History* showed a distinct tendency to circulatory disease, but otherwise was not remarkable.

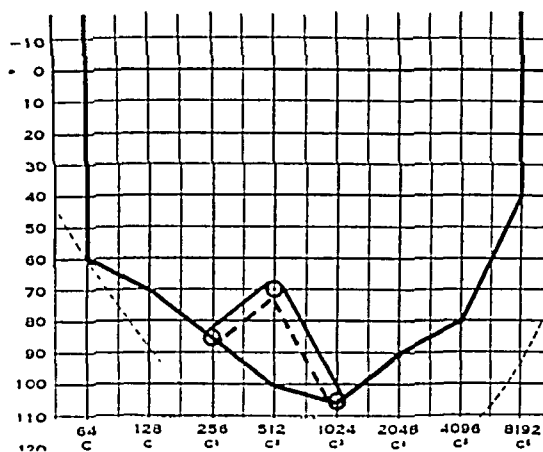
*Past History:* In addition to the diseases of childhood there is a history of neuritis in the neck; trauma to the head 19 years before with concussion; complete recovery in a week. Gonorrhea was contracted 20 years before, but apparently complete recovery took place. There has been some headache, occasional vertigo, and at one time frequent epistaxis. He has been married nine years; his wife has had several miscarriages and one child which died shortly after birth.

*Physical Examination* shows a well developed, fairly well nourished white male of 53. with somewhat doubtful teeth. Except for this and a minor cervical and inguinal adenopathy, the physical examination disclosed no abnormalities. At the time of the examination the patient was unable to receive communication except in writing.

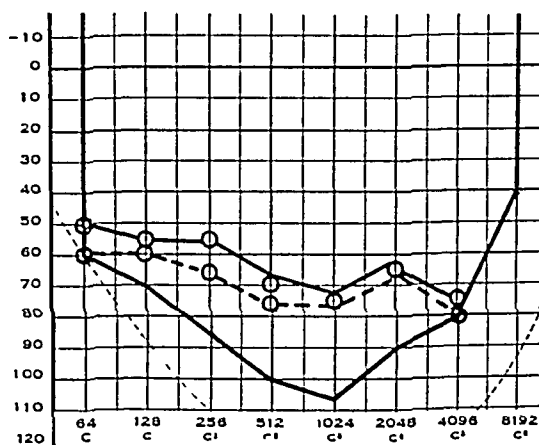
*Laboratory Summary:* The patient is 10 per cent underweight; the basal rate is low (—24 per cent), as is the pulse rate and the blood pressure. The urine shows casts and sugar. The protein intake is adequate; the partition formula, normal. The "urobilinogen" test is positive. Sugar tolerance is depressed. The nitrogen content of blood including the uric acid is increased. There is relative lymphocytosis. The serological tests were negative.

## PLATE 5

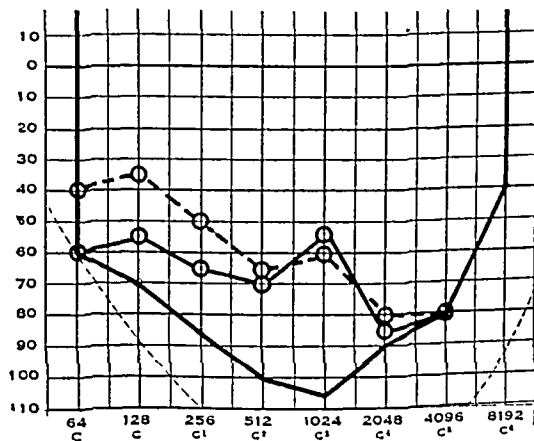
Case B-130. Pituitary disease with deafness.



No. 1. May 19, 1924.



No. 2. Dec. 19, 1924.



No. 3. Mar., 1928.

*Ear Examination:* The internal ears showed normal function. Some degree of stiffening of the drum heads and ossicles from chronic otitis media was noted.

*Neurological Examination* gave normal findings.

*X-Ray* showed sinusitis of frontals, ethmoid and antrum.

*Eye Examination* showed yellow discs, somewhat enlarged blind spots, and some cutting of the upper fields due to heavy, overhanging eyebrows.

*The audiogram* showed complete loss of hearing, except at 512 cycles, where there was slight residual acuity (see plates).

*Diagnosis:* The patient presented a definite sinusitis, gave evidence of lowered kidney permeability, a history in some respects suggestive of a specific eighth nerve involvement, but denied by several negative serological examinations. In addition, there was a suggestion of possible pituitary dysfunction of the common type (anterior lobe under-, posterior, over-active).

*Outcome:* He was given a therapeutic test with anterior lobe medication. In six months his hearing had improved markedly (see plate); he was able to understand conversation, and this condition has persisted, with possibly slight improvement in the speech area (see plate) up to the present time. Later incomplete examinations have shown a marked improvement in the laboratory picture, including a disappearance of the glycosuria.

## ASTHENIA

The next group to be considered is that in which asthenia was the principal difficulty. Cases have been selected illustrating two types, hypo- and dys-functional disorder of the pituitary. The laboratory data are given in the next table, as are those for two cases of headache.

**CASE B-28.** This patient was studied in the early days of these investigations and the records lack something of the completeness of the later reports. His chief complaint was of a marked fatigability, a slowing down and blunting of the mental processes, and ocular disturbances of a variable and intermittent character (v. i.). He had left college to accept a commission at the time of our entry into the war, served in the A. E. F., and after demobilization had resumed his interrupted studies. When first seen he was experiencing difficulty in completing a very elaborate academic program in which he had been engaged for several years.

*Family History:* Beyond a younger brother, who presented a retarded mental and physical development, the family history reported no abnormal individuals.

*Past History:* The patient reported the minor ailments of childhood, but gave a history of general good health and successful athletic activity until he entered the Army. He grew rapidly at or about the time of puberty and attained his height of six feet five inches while still a youth. During his army experience in France he devel-

oped a defect of vision, which was later shown to be due to a choroidal hemorrhage, producing a scotoma. After his discharge, as above stated, he resumed his studies and the remaining history was uneventful, except for the gradually progressive loss of physical and mental endurance.

TABLE XIV

		Asthenia		Headache	
		Number B-28	Number B-160	Number B-127	Number B-186
Diagnosis..	Anterior Lobe ...	—	—	—	+
	Posterior Lobe. .	—	+	+	+
Sex		Male	Male	Male	Female
Age	(yrs.). . . . .	27	38	29	31
Height . . . . .	(cm.). . . . .	195	183	163	170
Weight.....	(kgm.). . . . .	86.5	66.0	52.0	65.1
Weight . . . . .	Dev. (%).	-4	-14	-7	+1
Lung Volume. . . .	Dev. (%).	+18	-24	-11	-31
Basal Metabolism. .	Dev. (%).	-13	-7*	-15	+18†
Pulse. . . . .	(per min.). . .	56	72	57	74
Blood Pressure	(mm.). . . . .	118/64	120/82	102/64	124/84
Temperature ..	(deg. F.). . . .	97.1	97.2	97.4	98.6
Alveolar CO <sub>2</sub> ... .	(mm.). . . . .	55	44	33	—
Urine Volume . . . .	(c.c.). . . . .	2250	1360	1130	2000
Spec. Grav. . . . .		1.013	1.017	1.015	1.012
Albumin. . . . .		0	0	+	+
Casts.....		0	0	0	0
Sugar. . . . .		0	0	+	0
Total Nitrogen ..	(gms.). . . . .	13.48	10.92	11.16	13.46
Residual Nitrogen .	(%). . . . .	2.7	3.5	6.9	5.1
"Urobilinogen". . . .		+	+	0	0
Phen. Sulph. Phth . . . . .		90	56	67	36
Galactose Tolerance. .	Dev. (%). . . .	+67	-67	-67	-50
Non-Protein Nitrogen..	(mgm.). . . . .	31	42	36	37
Uric Acid.....	(mgm.). . . . .	4.9	4.8	4.2	3.0
Sugar.....	(mgm.). . . . .	88	104	73	86
Haemoglobin.....	(%). . . . .	95	95	95	100
Erythrocytes.....	(10 <sup>6</sup> )... . . . .	5.19	5.17	5.08	5.30
Leucocytes.....	(10 <sup>3</sup> )... . . . .	7.50	5.70	6.90	6.10
Lymphocytes.....	(%). . . . .	31	36	22	36
Eosinophiles.....	(%). . . . .	0	5	4	0

\* Not basal. Patient slightly restless.

† Slightly earlier test showed +40%, but patient nervous and test not basal.

*Physical Examination:* The patient was a symmetrically developed white male athlete, twenty-seven years of age. The face was the so-called pituitary type, the hands and feet large and well formed, the fingers long and tapering (type "en longe"). His general examination gave no abnormal findings, except for the eye condition to be discussed below, and a few minor varicosities in the lower limbs. This latter is a somewhat characteristic pituitary finding.

*Laboratory Summary:* His weight was but 4 per cent below prediction, his lung capacity 18 per cent above the most exacting (athlete) standard. The basal rate is below normal (the value —13 per cent is probably not exact, —20 per cent, obtained a few days

later, being more nearly basal); the pulse is slow. The urine was normal, save for a positive test for "urobilinogen." The sugar tolerance was much above the normal; the blood uric acid high; the blood morphology substantially normal.

*X-Rays* showed a normal sella and large frontal sinuses.

*Barany* tests showed intact and normally functioning labyrinths, with nystagmus unusually small in amplitude.

*Eye Examination* showed yellow discs, enlarged blind spots, and fields which were normal except where influenced by the scotoma. There was an absolute scotoma in the left side of the right field; a large absolute scotoma in the left field. In addition, there were several "moth eaten" areas in both eyes, due to degenerative changes in the retina and underlying choroid.

*Diagnosis:* The above picture defines a present bilobar hypofunction of the pituitary. The patient's physical habitus makes it seem probable that there was an early hyperactive phase at puberty, at least of the anterior lobe, which had spontaneously arrested.

*Outcome:* Medication with the components of the whole pituitary gland produced a marked improvement in the clinical picture, and he was able, not only to complete his academic program successfully, but to resume his athletic activities and row on a successful varsity crew. The eye condition has remained unchanged, the initial damage being permanent in its results.

**CASE B-160.** The patient's *Chief Complaint* was of marked asthenia, accompanied by severe supraorbital headaches. These were frequently associated with nausea and vomiting, relief following the latter. They came originally at monthly intervals, latterly every week or ten days. The whole condition was of some fifteen years' duration.

The *Family History* was not relevant, except for one sister, who died of diabetes.

His own Past History was almost equally negative. He had severe pneumonia at the age of two, and a temporary (?) cardiac disturbance, seemingly following severe influenza at the time of the epidemic. Beyond these, he has had no serious illnesses, but has never been robust. He has been married ten years; his wife has borne two children; she has had no miscarriages.

The *Physical Examination* showed heart and lungs normal; teeth show much dentistry; there is a minor inguinal adenopathy. The patient is six feet tall, a fairly well developed and nourished white male of thirty-eight.

*Laboratory Summary:* He is somewhat underweight and below his predicted lung volume. The basal rate is below normal (see table foot note); the urine gives a positive "urobilinogen" test; his sugar tolerance is markedly low; the blood uric acid is high, but the non-protein nitrogen is also somewhat above normal. The blood shows a slight relative lymphocytosis and 5 per cent eosinophilia.

*X-Ray* shows normal skull, sella and heart, some pulmonary fibrosis, and a single infected tooth.

*Neurological Examination* showed no abnormalities except a slight quantitative difference in the reflexes of the lower extremities.

The *Audiogram* showed slight but definite impairment of hearing (17 per cent).

*Eye Examination* recorded yellow discs, slight blind spot enlargement, and somewhat contracted fields.

*Diagnosis*:—The picture as given above defines a pituitary dysfunction with the characteristic formula.

*Outcome*: On the basis of this diagnosis anterior lobe *medication* was prescribed. The patient reported ten months later that his general level of endurance was practically normal, that he had had five months' freedom from headache, and in the remaining interval an occasional and not severe headache. A brief laboratory examination showed a normal basal rate, blood chemistry and morphology; no change in the audiogram, and practically normal eye findings.

## HEADACHE

CASE B-127. The patient originally came to the hospital with what was apparently an attack of renal colic. Physical examination, x-ray and other observations failed to substantiate the diagnosis, and the condition cleared up spontaneously during his hospital residence. He was transferred to us from the Surgical Service, as radiography showed a skull configuration suggesting acromegaly.

The present complaint is of headaches which began three years ago. Originally they were intermittent and relatively infrequent, but for some months past they have increased significantly in frequency and severity. They come over the right eye, but usually involve the whole frontal region, but do not radiate from this area. They are not associated with visual or gastric disturbances.

*Family History*: The patient was born in Russia and came to this country as a youth. He knows nothing of his family history except that he has five siblings living and well in this country.

*Past History*: The significant features are an earlier hospital admission for diabetes (undoubtedly a pituitary glycosuria); congenital (?) absence of a sense of smell; marked irregularity of the bowels, the usual interval being three or four days (seemingly a physiological peculiarity); some loss of hair from the vertex, but not from other parts.

*Physical Examination*: The patient is a well developed, slender white male of twenty-nine. The face and skull are markedly asymmetric with protruding, prognathous lower jaw. Some loss of hair over the ears is noted. The remaining findings are substantially normal.

*Laboratory Summary*: He is 7 per cent underweight; the basal rate is below normal; the pulse, blood pressure and temperature are moderately reduced; the urine shows sugar and albumin, but is otherwise normal, as is the nitrogen partition; sugar tolerance is much depressed; blood uric acid is high, and a leucoid blood with 4 per cent eosinophilia is present.

*Neurological Examination* gives substantially normal findings.

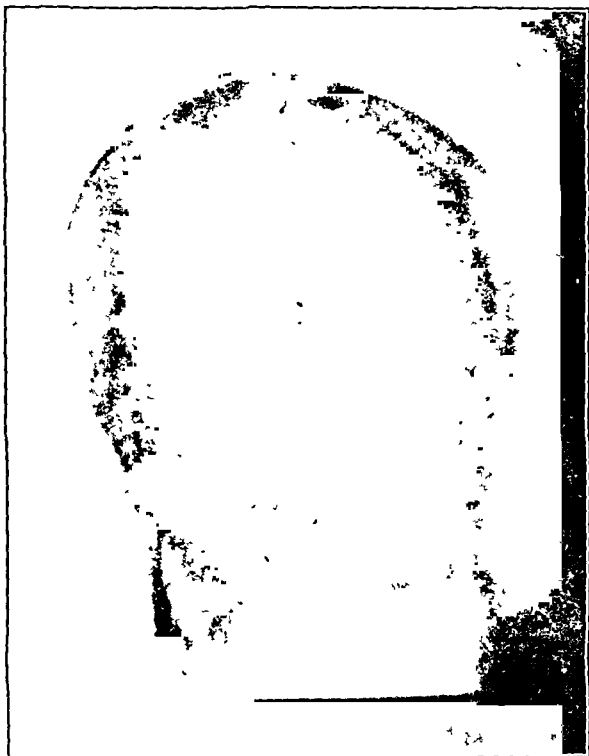
*Eye Examination* shows yellow discs, enlarged blind spots, and normal fields.

The *Barany* tests are normal.

*X-Rays* show normal heart, lungs and hands; infected teeth; very irregular and asymmetric skull with long prognathous jaw, prominent diploic veins and large frontal sinuses. The sella is small with heavy anterior and posterior clinoids (see plate).

PLATE 6

Case B-127. Anterior-posterior x-ray of skull.



The x-ray plates would seem to indicate that the lateral asymmetry of the patient's skull was repeated in the sella with an intrasella space like a truncated cone.

*Diagnosis:* The patient seems to present a case of aborted acromegaly, with the pituitary, at time of observation, in the characteristic dysfunctional state.

*Outcome:* The patient was placed on anterior lobe medication and for a time showed very definite improvement in his clinical condition. His grade of intelligence was rather low and after a time he

failed to follow his medication consistently. He then acquired syphilis and passed under other care.



Case B-127. Lateral x-ray of skull.

**CASE B-186.** The patient's chief complaint was given as headache complicated by polyuria and irregular menstruation. The headaches began at puberty, lasted from two to twenty-four hours, and came at irregular but frequent intervals. They were located in temples and vertex. Latterly they have been accompanied by vertigo and faintness. The polyuria began at fifteen and has been progressive except for a brief interval in 1918, following the influenza. The catamenia was established at thirteen, but was very irregular (increased interval) until seventeen, when they assumed a normal rhythm up to a year ago. At this time a tonsillectomy was performed, following which the patient has had but five periods, although the flow has increased somewhat.

*Family History:* The father is reported as having been an invalid all his life, to have been a sufferer from headache, and "to have suffered from one form of diabetes as a young man." The remaining history is irrelevant.

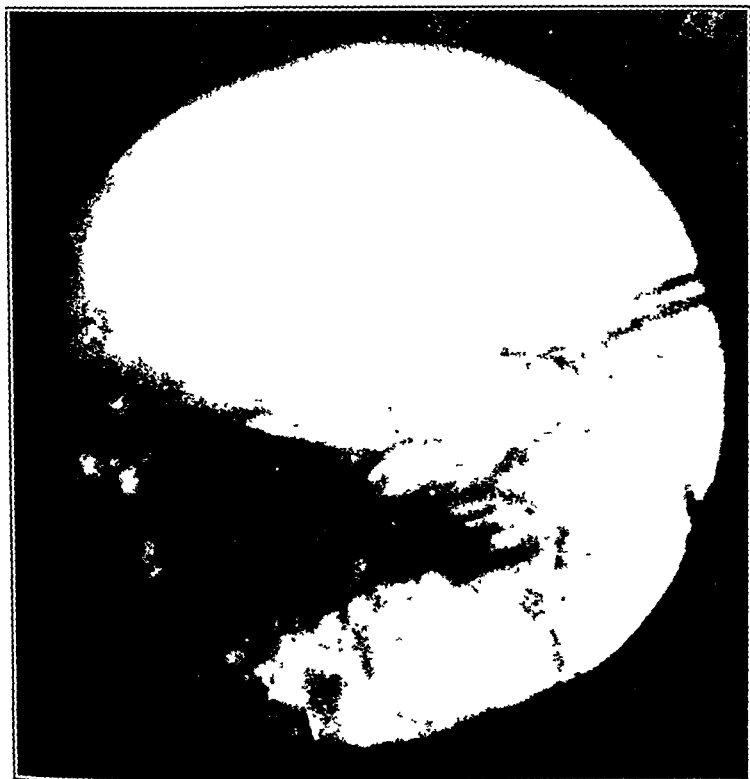
*Past History:* Beyond the facts already noted, there was a probable pneumonia; an attack of rheumatism a year ago, for which the



tonsil operation was performed; at this time a swelling in the neck in the neighborhood of the thyroid appeared, which "was reduced by x-ray"; some night sweats; otherwise nothing significant.

*Physical Examination:* The patient was a very well developed, tall, muscular white female of 31, of a distinctly masculine type. The facies is suggestive of the characteristic acromegalic formula. There is marked hypertrichosis with tendency to masculine distribution. There is a slight strabismus in the left eye. The breasts are small. There is slight dullness over the left lung (residual from the earlier pneumonia). Otherwise the findings are normal.

PLATE 6-a



Case B-186 Hyperpituitarism X-ray of sella.

*Laboratory Summary:* The basal metabolic rate is slightly above normal, the urine volume at this time ample, but not excessive, and otherwise normal except for albumin. Sugar tolerance was at half the normal level. The blood chemistry and morphology were normal.

The *Eye Examination* shows normal fundi, greatly enlarged blind spots (more in right) and significantly contracted fields.

The *Neurological Examination* gave no evidence of organic nerve disease.

A *Pelvic Examination* gave entirely normal findings.

*X-Ray* showed normal heart and lungs; the sella shows partial bridging of the posterior clinoids, but the cavity approximates the normal in size.

*Diagnosis:* On the basis of the above findings a diagnosis of bilobar hyperpituitarism was offered.

*Outcome:* As the condition did not seem of the utmost severity, operation was postponed and x-ray irradiation instituted.

The results of the first series of treatments can best be tabulated.

TABLE XIV-a

Date	Basal Rate	Wt. (kgm.)	Comment
December 15, 1924.....	+23%	66.0	Feels better
January 8, 1925.....	+17%	65.9	Feels better
January 15.....	+17%	65.5	Feels better
January 27.....	+11%	65.6	No more headaches
February 12.....	+16%	66.3	No more headaches
February 26.....	+ 8%	66.6	No more headaches
July 31.....	— 5%	66.1	No more headaches

After a period of practical freedom from headache there was a resumption, and treatments were again instituted, the basal rate having gone up to +20 per cent. This second series of treatments was effective, but there have been one or two further recurrences, all of which have responded to radiation. No complete studies have been made, but the eye examinations have been repeated at intervals. The latest (February 28, 1928) shows normal fields and blind spots, and the patient reports practical freedom from headache. The menstrual function has improved, though there is still some irregularity. Only the polyuria has failed to show real improvement and the patient still has intervals when she eliminates from 5,000 to 7,000 cc. daily. A possible explanation of this might lie in the persistence of an earlier damage to the mamillary bodies which is uninfluenced by the x-ray therapy.

## OBESITY

The next group of patients presents some interesting cases of obesity. The third of the group (B-92) is interesting as a case presenting an inversion of the usual dysfunctional formula. Certain significant data are collected in Table XV.

**CASE B-289.** The patient's chief complaint was obesity. Was obese as a child, but from the ages of eleven to nineteen had gained two hundred pounds at an apparently uniform rate. This would correspond to a weight of one hundred and thirty pounds at the age of eleven. The appetite is good, but is regarded by the patient as not excessive. He consumes a great deal of candy. He never perspires, except on the feet. He shaves only once a month, but the body hair is normal. He is nervously unstable.

*Family History* is irrelevant, except for a great uncle said to have been very stout.

*Past History:* He complains of occasional frontal headache; nothing else of significance.

*Physical Examination:* The patient is a tall, white male of nineteen, very obese and with marked tendency to girdle distribution. He has a short, thick neck and taper fingers. The genitalia are underdeveloped. The body hair is scanty. The abdomen is very heavy and pendulous. The remaining findings are normal. (See photographs.)

TABLE

	Obesity			
	Number B-289	Number C-29	Number B-92	Number B-293
Diagnosis.....	Anterior..... Posterior.....	— +	— +	— +
Sex.....	Male	Male	Female	Female
Age.....	19	11	43	27
Height..... (cm.).....	177	145	156	155
Weight..... (kgm.).....	150.0	160.5	98.4	114.1
Weight..... Dev.....	+123	+215	+88	+150
Lung Volume..... Dev.....	+4	-51	-24	-14
Basal Metabolism..... Dev.....	-9	-13	+14	-19
Pulse.....	64	62	87	60
Blood Pressure.....	124/62	188/80	134/98	118/74
Temperature.....	97.8	98.6	98.0	98.4
Alveolar CO <sub>2</sub> .....	39	46	40	42
Urine Volume.....	730	1030	620	910
Spec. Grav.....	1.030	1.026	1.018	1.020
Albumin.....	0	+	0	0
Casts.....	0	+	0	+
Sugar.....	0	0	0	+
Total Nitrogen.....	12.46	11.05	5.78	9.22
Residual Nitrogen.....	13.9	14.6	17.6	15.0
"Urobilinogen".....	0	+	+	0
Phen. Sulph. Phth.....	42	46	68	47
Galactose Tolerance..... Dev.....	+100	-33	+50	-50
Non-Protein Nitrogen.....	40	30	30	35
Uric Acid.....	4.9	5.2	4.4	4.3
Sugar.....	95	81	109	106
Haemoglobin.....	95	100	100	90
Erythrocytes..... (10 <sup>6</sup> ).....	4.88	4.80	5.53	6.74
Leucocytes..... (10 <sup>3</sup> ).....	5.90	8.40	10.70	7.30
Lymphocytes..... (%).....	42	36	27	34
Eosinophiles..... (%).....	2	3	2	2

*Laboratory Summary:* The patient is 123 per cent overweight. His basal metabolic rate is slightly low. The residual nitrogen is high. His sugar tolerance is twice the normal; the blood uric acid is high; the blood is lymphoid in type.

X-Ray shows undeveloped frontal sinuses, shallow sella, normal heart and lungs.

PLATE 7



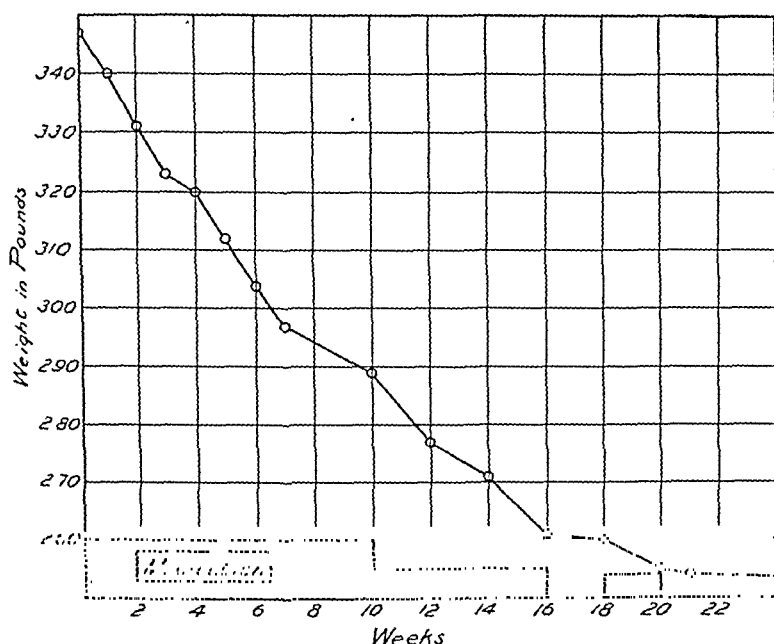
Case B-289.

*Neurological Examination* shows no abnormalities.

*Eyes* show yellowish discs, slight blind spot enlargement, and very slight form field contraction.

*Diagnosis:* The findings indicate a bilobar pituitary failure.

*Outcome:* The patient was placed on the appropriate medication after an interval in which his weight increased to 347 pounds. With some dietary restriction and glandular therapy, the weight loss progressed as shown in the accompanying graph. It will be noted that with suspension of medication the loss of weight stopped. After the twentieth week he discontinued the medication, and at the end of thirty-one weeks (not shown on the chart) he had begun to gain. His weight at this time was 258 pounds.



Case B-289. Change of weight with pituitary medication.

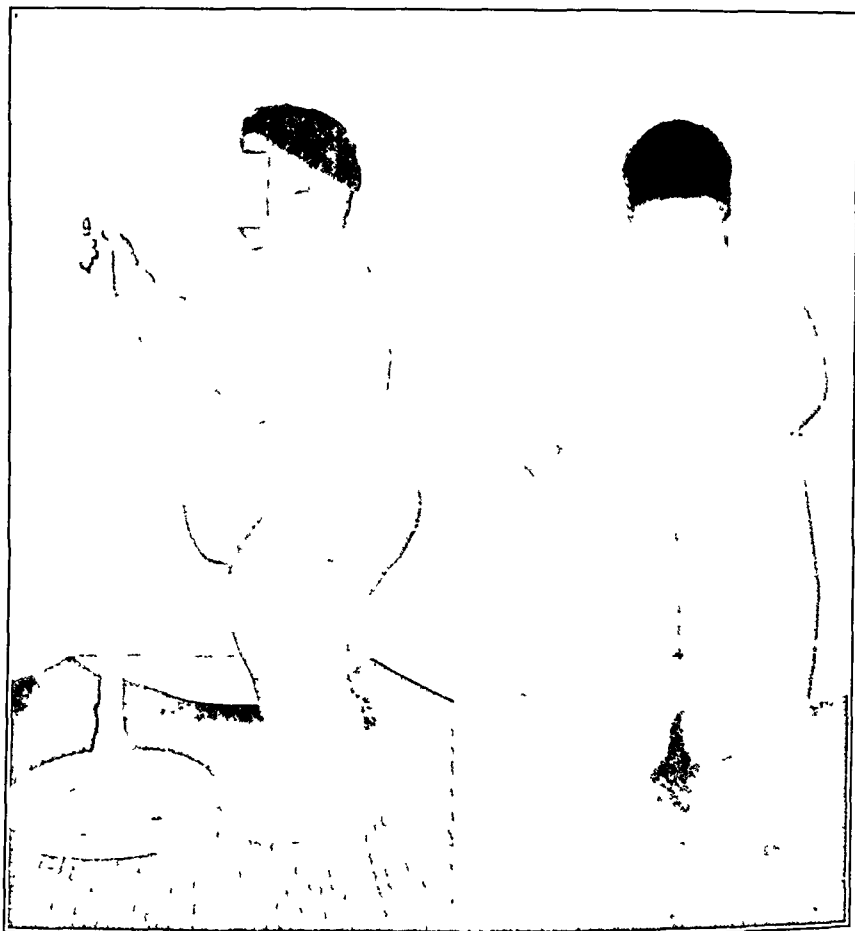
CASE C-11, 29, 37, 39. The patient's chief complaint was obesity. At the time of first contact he weighed about 165 kgm. and was 145 cm. tall. He weighed 3.8 kgm. at birth, but began to grow fat at once, so that at six months he weighed 27 kgm. Some time elapsed between his first contact and the first examination; his weight on first admission was 163.5 kgm. A preliminary study was made in February, 1925, which was incomplete (lack of co-operation), but enough data were secured to warrant a tentative diagnosis and medication and diet were suggested. Nine months later an older brother called upon us and gave the information that nothing had been done but dietary restriction at irregular intervals. At his request the patient was

re-admitted in November, 1925, and the first complete study (C-29) carried out.

*Family History:* The mother weighed 200 pounds, but all other members of the family were well built and not obese. The remaining history is not relevant and is not entirely reliable.

*Past History:* All of the minor ailments, scarlet fever and diphtheria are reported. He had abscess on the neck requiring drainage. He complained of headaches during which the eyes are "sore." He

PLATE 8



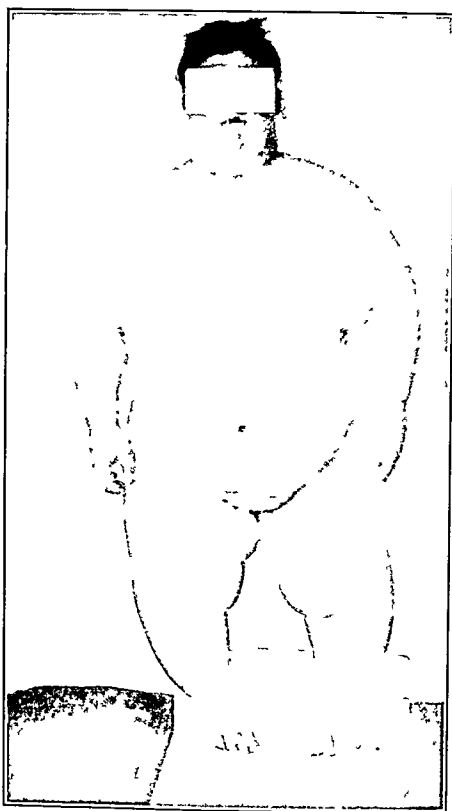
Case C-29. No 1

No. 2

had marked dyspnoea and palpitation; polyphagia; nocturnal enuresis; occasional incontinence in the daytime. He is easily fatigued and frequently rests by kneeling on one knee. He is of apparent average mentality.

*Physical Examination:* The patient was an enormously fat Italian boy of eleven. The head was very large and the fat of the

scalp could be picked up in folds. Diffuse acniform eruption and many blackheads were present. The breasts were very large. The heart and lungs were hard to define, but apparently normal. The abdomen forms a pendulous apron. But one small testicle is palpable in the large scrotum; there is seen some black pubic hair. He has small hands and feet with tapering fingers. There is maceration on all body surfaces lying in apposition (see photographs).



Case C-29. No. 3

*Laboratory Summary:* The boy was 215 per cent above his predicted weight, and as his sitting-height index was 0.561 this was below the truth. The lung capacity was but one-half of prediction. His basal rate was —13 per cent (earlier figures gave a mean of —20 per cent), with high systolic blood pressure. (Independent measurements at this time indicated that the true blood pressure was about 145/80.) The urine showed albumin and casts; the residual nitrogen fraction was definitely high; the "urobilinogen" test was repeatedly positive. The sugar tolerance at this time was somewhat depressed; blood uric acid decidedly high. There was a slight lymphocytosis (?), and 3 per cent eosinophilia.

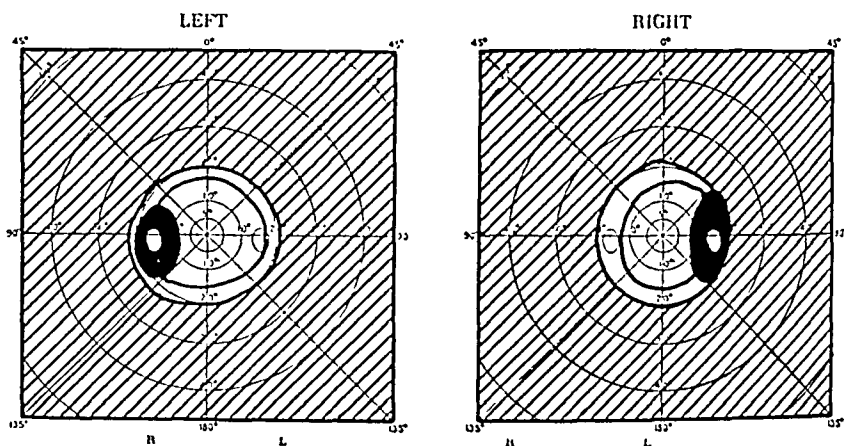
*Neurological Examination* showed a slowing of the mental processes without arrest of mental development.

*Eye Examination* showed stiff pupillary reactions, choked discs (4 diopters), very marked contraction of fields (see plate), and greatly enlarged blind spots.

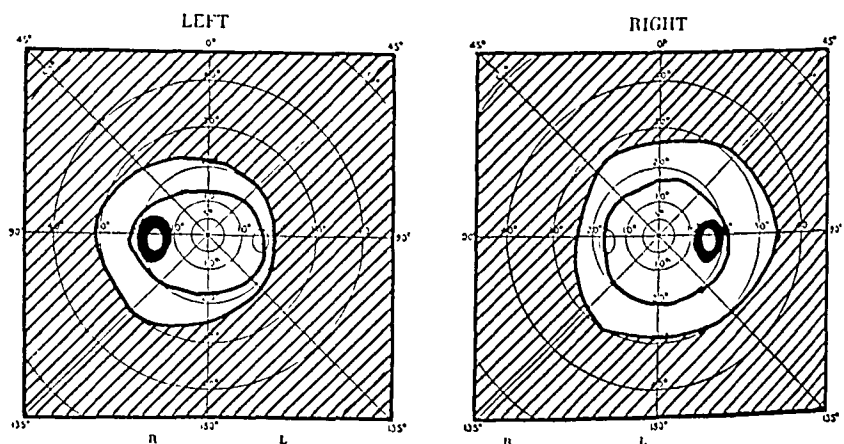
*X-Ray* showed infected teeth, normal sella (3 sets of plates) and thick skull wall.

*A Mosenthal test of kidney function* showed normal concentrating power.

*An Audiogram* showed some loss of hearing, most pronounced in the middle range.



No. 1 Nov. 5, 1927.



No. 2. June 25, 1927.

*Diagnosis:* A diagnosis of pituitary dysfunction with anterior lobe over- and posterior under-active was established.

*Outcome:* Anterior lobe medication with dietary restriction was prescribed. Because of the choked discs, a lumbar puncture was performed, the pressure of the fluid being in excess of 300 mm. The



laboratory examination gave normal findings. The patient was placed on Epsom salts and repeated eye examinations were made. Four weeks after the puncture the report was "practically no elevation of discs, cups clearly defined, no hemorrhage, and lymph stasis almost cleared up." During this month the patient lost eighteen pounds. After a further hospital stay, during which time medication and diet were followed, with definite weight reduction (ca. 135 kgm), the patient was discharged. He returned in May (1926) for a check up. The findings showed that neither diet nor medication had been carried out; the weight was 142.3 kgm., the basal rate —22 per cent, and the sugar tolerance unchanged. The other findings reflected the earlier therapeutic measures in more nearly normal levels. The eye findings showed no return of the choked discs; the right blind spot was smaller, the contracted fields unchanged. The parents were urged to continue the medication and diet and the boy sent home. He returned in February, 1927, giving every evidence of complete absence of any care (confirmed later by a member of the family). He had regained all of his lost weight (165.5 kgm.), the basal rate was —23 per cent, the sugar tolerance unchanged (—33 per cent). The left eye had maintained the earlier improvement; the right showed a slight return of the choked disc, but the fields were better and the blind spot smaller (see plate). Recognizing that nothing could be done for him in his home, with the consent of the parents he was placed in a state institution. They were unwilling to let him remain, however, and again took him home. The present status of the case is unknown.

**CASE B-92.** This case has been selected for the unusual dysfunctional formula presented.

The patient's chief complaints were obesity; unilateral deafness; palpitation and vertigo intensified at the time of her periods. The first condition was of long standing and had been gradual in its progress; the deafness followed childbearing; the other conditions date from a nervous breakdown a year earlier.

*Family History:* Beyond a familial tendency to tuberculosis, the history is not significant.

*Past History:* Minor ailments in childhood, mumps without complications in her early thirties, and a susceptibility to infections of the respiratory tract were reported. She stated that she had polydypsia and polyuria, but gave no evidence of these during hospital stay. The catamenia was established at eleven, the periods being regular and normal in amount. She has been married for a number of years and has borne three children without miscarriage.

*Physical Examination:* The patient was a white woman of forty-three, extremely obese and with a tendency to girdle distribution. The remaining findings were normal.

*Laboratory Summary:* She was 88 per cent overweight; the basal rate was slightly high (several wholly concordant observations); there were somewhat rapid pulse; urine scanty; very high residual nitrogen; positive "urobilinogen"; increased sugar tolerance; high blood uric acid; the blood morphology was normal.

*Neurological Examination* showed involvement of the vestibular portion of the eighth nerve. Otherwise the findings were normal.

A Barany test shows hypersensitivity of the labyrinth.

*Ear Examination* shows no anatomical changes.

## PLATE 9



Case B-92.

*X-Ray* shows normal skull, sella, and chest.

*Eye Examination* shows over-filled veins in fundi, slight blind spot enlargement, and normal fields.

*Diagnosis:* The sugar tolerance is consistent only with a posterior lobe failure or a hypothyroidism of marked degree. This latter is denied by the basal rate. Substantiating observations are the high blood uric acid, the positive "urobilinogen," and the relatively normal levels of many of the other findings. The basal rate is on the upper side of the normal range. Coupled with the somewhat rapid pulse, it is consistent with a very slight overactivity, which is probably merging downward to an ultimate hypofunctional level. A diagnosis of pituitary dysfunction with the anterior lobe over- and posterior under-active was offered, and posterior lobe *medication* recommended.

*Outcome:* The patient left the state, but a year later opportunity for a partial check up showed a loss of over 20 kgm., a normal basal rate (—2 per cent), and marked clinical improvement.

CASE B-293. This case has been selected because the patient shows the most striking conformity to the conventional formula of fat distribution of the entire series (see photographs). Her chief complaint was of obesity, in addition to which she had a history of convulsions and complained of pain in the lower spine. During the first six years of her marriage she was infertile, and at the end of this period she weighed 64 kgm. In the past five years she has borne four children and had two miscarriages, with a steady increase in weight to her present level of 114 kgm. She has had two operations for the removal of abdominal fat. She stated that for the past year she has had sharp pain and tenderness in the lower spine. The convulsions started three weeks earlier. There is a preliminary sense of pressure over the left chest, and headache, followed by a gradual loss of consciousness; there ensues a tonic spasm of the body lasting no more than a minute or two and accompanied by grinding of the teeth. Several of these spasms occur during the period of unconsciousness and the attack terminates with gradual relaxation. Morphine is the only drug that has proven effective, and the patient was under a heavy morphine dosage at the time of her entrance. Seizures observed during her stay in the hospital did not conform entirely to this formula; there was prompt and complete recovery and the substitution of occult non-narcotic therapy yielded excellent results.

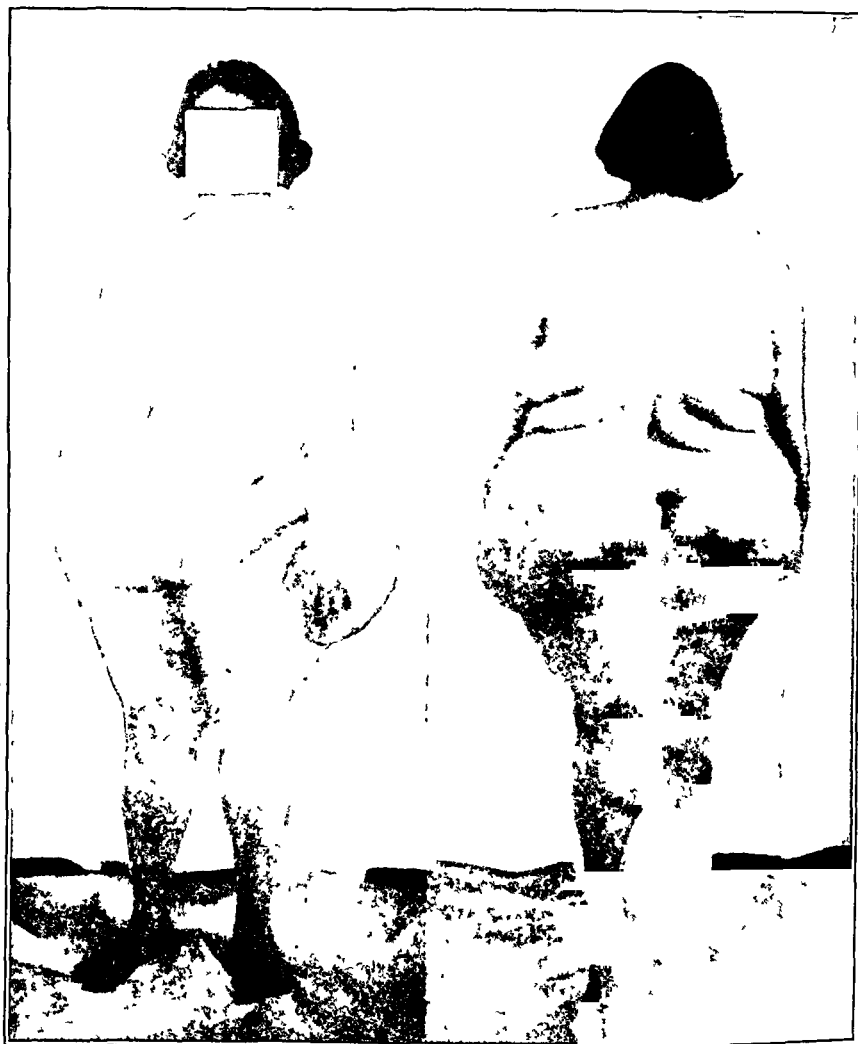
*Family History* is entirely irrelevant.

*Past History:* Beyond minor ailments and the facts stated above, the patient had four gall stone operations, the last being removal of the gall bladder. The catamenia was established at eleven and the periods were entirely normal up to the time of her five-year amenorrhea determined by her repeated pregnancies. It is interesting to note that she always conceived before the re-establishment of her periods following childbirth.

*Physical Examination:* The patient was a white woman of 27, with delicately moulded features, hands, feet, forearms, and lower legs, but with an enormous fat deposit in the middle third of the body. The breasts were very large and pendulous. There was a marked post-operative hernia. The remaining examination, including the spine, gave entirely normal findings.

*Laboratory Summary:* The patient was 150 per cent overweight, with basal rate below normal. The urine showed casts, sugar, and a high residual nitrogen fraction. The galactose tolerance was reduced to half the normal level; the blood uric acid was high; there was a slight relative lymphocytosis. A few of the patient's measurements are striking.

PLATE 10



Case B-293. No 1.

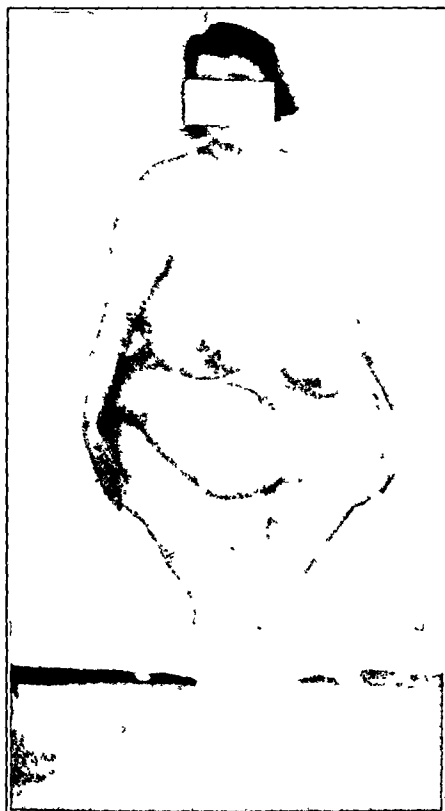
No 2.

*X-Ray* showed normal skull and sella.

*Neurological Examination* offered no evidence of organic nervous disease. The seizures were believed to be hysterical in character or possibly of toxic origin deriving from an endocrine condition.

TABLE XV-a

Chest .....	109	cm.
Waist .....	110	cm.
Hips .....	160.5	cm.
Upper arm.....	Right 40	Left 42
Forearm .....	Right 25	Left 25
Wrist .....	Right 15	Left 15
Thigh .....	Right 81	Left 79
Calf .....	Right 41	Left 39
Ankle .....	Right 21.5	Left 20.5



Case B 293 No 3

*Eye Examination* showed yellow discs and so great a symmetrical contraction of the fields (10 degrees) that the blind spots could not be delineated.

*Diagnosis:* The picture given above defines a pituitary dysfunction of the usual type. Anterior lobe medication was advised, but the patient passed out of our knowledge after showing some improvement.

An interesting feature is the patient's fecundity after a six-year sterile period.

## STERILITY

An interesting group of cases are those exhibiting sterility, apparently the result of pituitary malfunction, as they become fecund with the correction of the endocrine impediment. This whole question is now under extensive investigation and will be reported in detail at a later date. A single typical case is reported in the next table (Table XVI). In this table are given two series of observations on the same patient which illustrate the tendency to functional involution which this glandular structure frequently undergoes. Although a diagnosis was estab-

TABLE XVI

	Sterility	Progressive Change		Growth Arrest	
	Case No. S-260	Case No. B-162	Case No. B-162-a	Case No. B-190†	Case No. S-1605†
Diagnosis... . Anterior... Posterior...	— ?	— +	— —	— N	— +
Sex.....	Female	Female	Female	Male	Male
Age..... (yrs.).....	34	36	38	16	19
Height..... (cm.).....	181	160	160	132.5	150.6
Weight..... (kgm.).....	88.3	76.8	80.7	22.0	35.0
Weight Deviation..... (%).....	+20	+22	+28	-34	-25
Lung Volume Dev..... (%).....	-24	-24	—	-16	-24
Basal Rate Dev..... (%).....	+2*	-12*	-8*	-17	-20
Blood Pressure..... (mm.).....	134/92	112/68	106/58	90/52	96/40
Pulse..... (per min.)...	62	68	57	68	60
Temperature..... (deg. F.)...	97.4	97.5	97.9	98.1	97.8
Alveolar CO <sub>2</sub> ..... (mm.)...	35	—	—	40	40
Urine Volume..... (cc.).....	1640	2440	1450	370	410
Specific Gravity.....	1.016	1.009	1.015	1.023	1.028
Albumin.....	0	+	0	0	+
Casts.....	0	+	0	0	0
Sugar.....	0	0	0	0	0
Total Nitrogen..... (gms.)...	12.47	8.97	8.96	4.78	5.28
Residual Nitrogen..... (%)...	3.8	10.1	9.3	21.8	11.0
"Urobilinogen".....	+	+	0	0	0
Phen. Sulph. Phthal... (%)...	55	32	75	30	58
Galac. Tol. Dev..... (%).....	—	-75	> +50	±0	-33
Non-Protein Nitrogen..... (mgm.)...	24	39	—	29	32
Uric Acid..... (mgm.).....	5.0	2.4	3.6	2.2	2.7
Sugar..... (mgm.).....	130*	94	98	89	91
Haemoglobin..... (%).....	95	90	90	90	85
Erythrocytes..... (10 <sup>6</sup> ).....	4.76	5.31	4.91	4.66	5.00
Leucocytes..... (10 <sup>3</sup> ).....	7.90	9.25	6.15	5.45	8.15
Neutrophiles..... (%).....	33	53	70	38	56
Lymphocytes..... (%).....	57	44	24	55	39
Eosinophiles..... (%).....	0	0	2	3	1
Monocytes..... (%).....	10	3	4	4	4

\* Too high. Patient nervous.

† September, 1924.

‡ September, 1927.

lished during the first contact, the patient declined to undergo medication and the later series of tests were uninfluenced by any intermediate therapy.

**CASE S-260.** The patient's chief complaint was sterility, her six years of married life with constant exposure having failed to produce pregnancy. Her husband has been shown to be fertile.

*Family History* was irrelevant.

*Past History:* The patient records minor ailments, a period of rapid growth from eleven to fourteen, at which age she established the catamenia. This latter is not remarkable except for scanty periods and headache. She was married at twenty-eight and shortly thereafter gained thirty pounds in weight. She has been fatigable; has never had much perspiration, although she feels the heat markedly. Two years ago she was given ovarian extract which produced benefit in her general condition, but had to be discontinued, as it produced palpitation.

*Physical Examination:* The patient was a very tall white woman of thirty-four, with a definite "girdle" obesity. The remaining findings were normal.

*Laboratory Summary:* The report is incomplete, since full co-operation could not be secured. She was 20 per cent overweight. The basal rate was not satisfactorily determined, but undoubtedly below the normal level. The urine was practically normal, except for a positive "urobilinogen." She had high blood uric acid and markedly lymphoid blood. The sugar tolerance could not be determined.

*X-Ray* showed bony bridging of the sella.

*Eye Examination* showed yellow discs, slightly enlarged blind spots, and a contraction of the red fields.

*Diagnosis:* Recognizing the numerous omissions from the diagnostic picture, a tentative diagnosis of pituitary disease was based on the available information. The anterior lobe was construed to be underactive; the posterior was undetermined.

*Outcome:* The patient was placed on anterior lobe medication and inside of three months became pregnant, ultimately delivering a normal child.

**CASE B-162, 162-a.** This case is presented as showing the natural course of a pituitary disorder uncomplicated by glandular therapy. The patient was first seen in May, 1924.

Her chief complaints were of some frontal headache, fatigue and gastro-intestinal disturbance. She dates the onset from an operation for the removal of a tube and ovary, the other uterine adnexa having been removed eighteen years previously. As a matter of fact, while a laparotomy was performed, the ovary was not removed and the patient has continued to menstruate up to the present, a fact that seemingly has not appeared to her to be inconsistent with her supposed condition. The headaches originated in the frontal region and radiated backward. They were chiefly associated with her periods. The fatigue was continuous and unrelieved by eighteen hours' continuous sleep in which she frequently indulged. She had frequent

attacks of excessive perspiration; there were frequent attacks of nausea and vomiting, which began after her first pelvic operation (18 years ago). In the last three years there have been intermittent attacks of diarrhoea. In addition, there were numerous minor complaints.

*Family History:* Completely irrelevant.

*Past History:* The patient had scarlet fever and several minor ailments in childhood. Nine years ago she was in bed for sixteen weeks with an attack which began with headache, vomiting, and fever, caused complete paralysis of the lower limbs and from which she recovered completely. She weighed 53 kgm. at thirty-two, and at the time of this study, four years later, 76.8 kgm. In addition to those given above, she had some operation on the bladder fourteen years ago. She had chronic cough from the age of nine. She matured at twelve years, the first period following a dilation. Menstruation was irregular with shortened interval to eighteen; since then it has been regular at twenty-day intervals with five-day periods. She has been married eighteen years with three pregnancies, resulting in one premature birth, one miscarriage, and one full term, normal child.

*Physical Examination:* The patient was a well developed white female of thirty-six, obese and with marked tendency to girdle distribution. The teeth were very poor; lungs normal. Some varicosities were noted in the lower limbs. Neurological and other findings were normal.

*Laboratory Summary:* The patient was 24 per cent overweight. On account of nervousness, a satisfactory basal rate determination could not be secured; the observed value was below the normal level. There were moderate reductions in the physical measurements; high urine volume; albumin and casts present; high residual nitrogen; positive "urobilinogen"; galactose tolerance greatly reduced; phthalain test low. The blood morphology showed lymphocytosis and 3 per cent eosinophilia.

*X-Ray* showed normal skull and sella and obscured frontal sinus. There was evidence of healed and calcified lymph nodes at the left apex and a calcified gland in left hilus.

*Pelvic Examination* showed an intraligamentous cyst in the right vault, but otherwise no abnormalities.

*Eye Examination* showed marked symmetrical contraction of fields and enlarged blind spots.

*Diagnosis:* This general picture was felt to define a pituitary dysfunction of characteristic formula.

*Outcome:* Anterior lobe medication was advised. The patient declined treatment, however, but returned in January, 1926. A partial study was carried out. She had gained some 4 kgm. in weight; again a satisfactory basal rate determination could not be secured, but the observed value left no doubt as to the hypofunctional level of the anterior lobe. The complementary physical findings were slightly lower (temperature excepted); the earlier kidney condition had apparently cleared up entirely, her sugar tolerance had increased to a level over 50 per cent above the normal (she would not complete this test), the blood uric acid was relatively higher, but still normal; the blood had become leucoid in type, with a 4 per cent eosinophilia. The

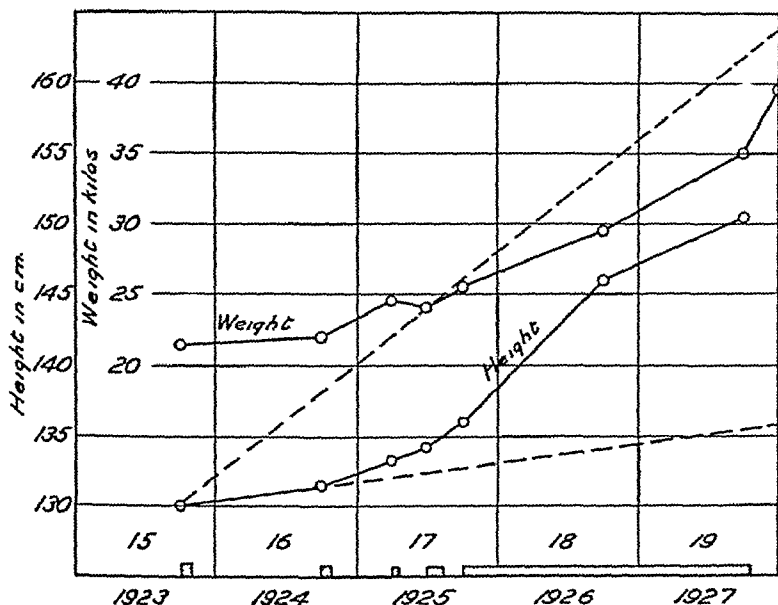


eyes showed further contraction of the fields and enlargement of the blind spots. X-ray findings were unchanged. The general condition was unchanged.

Obviously, the posterior lobe had undergone functional involution during the interim, and the patient had become a bilobar failure. Appropriate medication was recommended, but contact was lost before the outcome could be ascertained.

CASE B-72, 190, C-12, Sp 25-a-b-c, S-1605. This patient was first seen in September, 1923. A partial study was made, a tentative diagnosis of pituitary dysfunction established, and a brief course of anterior lobe medication instituted. The boy grew an inch during his hospital stay and was sent home to continue his therapy. He returned a year later. It was found that he had made no progress, and enquiry developed the fact that he had had no medicine. A complete study was made (see B-190 in Table XV) and the original diagnosis confirmed.

PLATE 11



Case B-190 Change of weight and height under influence of pituitary medication.

His chief complaint was of inability to swallow. This kept him undernourished. He was also much below the normal height for his years. He had been in good health and large for his age up to 7½ years. He then developed whooping cough and it was stated that the medicine used at this time provoked attacks of vomiting, which continued for one year. Following this, radioscopy disclosed an œsophageal stricture, and three years ago he was dilated, with temporary relief. His difficulty in swallowing is intermittent; at times solids can be taken and at others, even liquids cannot be swallowed. From

the time of the whooping cough he grew very slowly, so that he was much undersize for his age. He was referred to us for his dwarfism and for an apparently persistent thymus, disclosed by the x-ray.

*Family History* was irrelevant.

*Past History:* Beyond the facts recorded above, there is little of importance.

*Physical Examination:* The patient was a white boy of sixteen, greatly undernourished and looking like a child of eight. His mental age corresponded to his actual years. The head was disproportionately large. The testes were descended but very small. The genitalia were infantile in type. Beyond a minor cervical adenopathy nothing of importance was observed.

*Laboratory Summary:* The patient was 34 per cent underweight, with normal sitting height index. The basal rate was 17 per cent below prediction; blood pressure low; respiration somewhat slow. The urine showed poor elimination, but this was undoubtedly due to his low intake. Protein intake was inadequate and the residual nitrogen fraction was very high. The phthalein test was distinctly low. The sugar tolerance at this time was normal; the blood chemistry normal; the blood morphology showed a marked lymphocytosis and 3 per cent eosinophilia.

*X-Ray* examination showed a substernal shadow to the right of the spinal border; undeveloped carpal scaphoid; an unformed trochlear process of the lower end of the humerus; unformed olecranon; normal skull and sella; cardiospasm—obstruction to barium meal at cardia.

*Eye Examinations* showed stiff pupillary reflexes, the other findings being substantially normal.

*Diagnosis:* The genital arrest, the retarded ossification, the dwarfism, and the persistent thymus, all pointed to a developmental arrest. His symmetry and good proportion coupled with the laboratory findings pointed to a pituitary dysfunction in which the anterior lobe was underactive and the posterior, normal, at the time of observation. As there exists no satisfactory evidence of the endocrine property of the thymus—and much to deny it—it was felt that the persistence of this gland was but one more evidence of an arrest in normal developmental changes.

*Outcome:* Anterior lobe medication was again applied for a brief space and the patient discharged with the recommendation to continue it. This was not done, however, and during the succeeding year we had several contacts with the patient at each of which some anterior lobe was given to which he responded (See Graph). At the last of these, finding that his medication ceased when he left the Hospital, we arranged for a regular supply to be sent to him. During the first two years he had gained 6 cm. on an occasional brief period of pituitary (anterior lobe) medication; during the next two with more consistent therapy and in spite of presumptively lowered growth capacity, he has increased 14.6 cm. In the accompanying graph are shown the weight and growth curves over the interval. The dotted lines represent extrapolations, and naturally are devoid of real significance, but are possibly suggestive. The lower shows the predicted height at present had the growth rate of the first year persisted; the

upper, the prediction had the boy enjoyed the benefit of adequate medication from the beginning.

During 1925 the boy developed a slight general adenopathy. A biopsy was performed but the tissue removed gave no clear-cut evidence of the presence of Hodgkin's disease. The latter history would render this condition highly improbable.

*Nose and Throat* findings were normal.

An *Audiogram* showed a slight loss of acuity in the speech area.

He has had a complete laboratory check up at yearly intervals, the data from the latest being given in Table XVI. It will be noted that his basal rate is still below prediction, and this is due to the impossibility of grading the dosage to his needs under the conditions imposed upon us. The throat condition has cleared in large measure, but is not entirely corrected. This has determined the low nutritional intake which has undoubtedly influenced his growth curve on the one hand and his urine elimination picture on the other. The residual nitrogen fraction is approaching normal limits. The phthalein output is now normal, and indication of a better general metabolic level. The sugar indicates a present slight overactivity of the posterior lobe. This has fluctuated during the period of observation, at times being over-, at times under-active. At no time has there been an over supply of the active agents of the anterior lobe, though the degree of hypofunction has fluctuated with the medication and the patient's needs. The lymphocytosis, while still in evidence, is significantly decreased.

*X-rays* show a mediastinal shadow below and behind the sternal notch; the heart gives some evidence of dilation.

An *Eye Examination* gives normal findings except for yellow discs, the pupillary reflexes being entirely normal. "Urobilinogen" was noted at times in the urine but has apparently disappeared. The earlier adenopathy has largely cleared up. Clinically, the boy is greatly improved, is now in college, and doing very well.

*Comment:* In reviewing this case one cannot but regret that sustained controlled therapy could not have been followed from the beginning. It is idle to speculate as to results, but with those obtained by highly irregular treatment it may be assumed that the salvage would have been even greater.

## EVOLVING ACROMEGALY

CASE S-326, 326-a, B-269, 269-a, 475, 475-a, 475-b, 475-c: This case has been under almost constant supervision since 1924. While it will be reported at length elsewhere in the near future and certain phases of the carbohydrate metabolism have recently been completed by one of our colleagues [Ulrich (54)] it presents certain points of such marked interest as to warrant brief presentation here. The patient is still under observation.

The patient was first seen in July, 1924; he was a powerfully built young man of twenty-four with the typical facies of acromegaly. The chief complaint was of recurrent paroxysmal headache which began in 1921 with increasing frequency and intensity during the interim.

*Family History* is entirely irrelevant.

*Past History:* Beyond a few minor ailments and a recent tonsil and adenoid operation, the history was entirely uneventful. A photograph taken in 1916 gives no evidence of acromegaly, but one at twenty, a year before the onset of symptoms, shows well marked and typical changes.

*Physical Examination:* The patient was a powerfully developed, well nourished white male of twenty-four. The hands were large, the feet of normal size. There was marked generally distributed pilosity. The reflexes were present but somewhat sluggish. The remaining findings were completely normal.

TABLE XVII

		July, '21	Dec., '21	Feb., '25	July, '25	Mar., '26	Dec., '26	Sept., '27
		Case No. S-326	Case No. -326-a	Case No. B-269-a	Case No. B-475	Case No. B-475-a	Case No. B-475-b	Case No. B-475-c
Diagnosis.	Anterior . Posterior. .	- -	+ +	+ +	- +	N +	+ +	+ +
Sex		M	M	M	M	M	M	M
Age	(yrs.)	21	25	25	25	26	27	28
Height.	(cm.)	172	172	172	172	172	172	172
Weight.	(kgm.)	83 1	81 2	82 5	87.5	80 5	77.0	69.2
Weight Deviation	(%)	+21	+19	+20	+28	+18	+8	-3
Lung Vol. Dev.	(%)	+9	+1	-2	-3	-21	-2	-21
Basal Rate Dev.	(%)	-11	+65	+12	-7	+4	+28	+54
Blood Pressure	(mm.)	110 55	118/72	130/58	106/60	100/80	106/58	120/78
Pulse.	(per min.)	53	91	68	62	69	76	78
Temperature	(deg. F.)	97 9	97 8	98 0	97 6	98.0	97.8	98 0
Alveolar CO <sub>2</sub> .	(mm.)	-	13	11	15	42	48	44
Urine Volume	(cc.)	1010	7920	1950	1740	2140	1890	1540
Specific Gravity		1 017	1 031	1 018	1.011	1 027	1 037	1 038
Albumin.		0	0	0	+	+	0	0
Casts..		0	0	0	0	0	0	0
Sugar.	(gm.)	0	238	0	0	133	74	78
Total Nitrogen.	(gms.)	7 66	23 92	13 94	11.44	12.75	11 55	4 28
Residual Nitrogen.	(%)	5 2	1 8	5 5	9.5	13 9	11 9	3 8
"Urobilinogen".		0	0	+	0	0	0	0
Phen. Sulph. Phthal	(%)	46	68	16	16	43	48	44
Galac. Tol. Dev	(%)	+33	-	-33	-67	-67	-83	-67
Non-Pro. Nitrogen	(mgm.)	35	59	27	32	27	26	33
Uric Acid....	(mgm.)	5 1	6 6	3 7	4 3	3 0	4.7	2.4
Sugar.....	(mgm.)	102	104	99	103	364	334	510
Haemoglobin..	(%)	100	85	80	100	100	90	98
Erythrocytes..	(10 <sup>6</sup> )	5 70	5 12	4 36	5 69	6.07	5 18	5 26
Leucocytes....	(10 <sup>3</sup> )	9 75	10 40	8 25	11 36	11.50	11 30	21 60
Neutrophiles....	(%)	17	54	16	57	52	53	67
Lymphocytes....	(%)	44	39	18	38	40	38	30
Eosinophiles....	(%)	5	6	3	2	5	2	1
Monocytes....	(%)	4	1	3	3	3	7	2

*Laboratory Summary:* The patient was 21 per cent overweight, with basal rate of -11 percent, blood pressure slightly low and pulse slow. The urine presented a normal picture throughout. The galactose tolerance was slightly high; the blood uric acid definitely above normal; the blood was lymphoid with a 4 percent eosinophilia.

*X-Ray* showed an enlarged sella with shallow, eroded floor (see plate) and large frontal sinuses.



Case S 326. Before onset

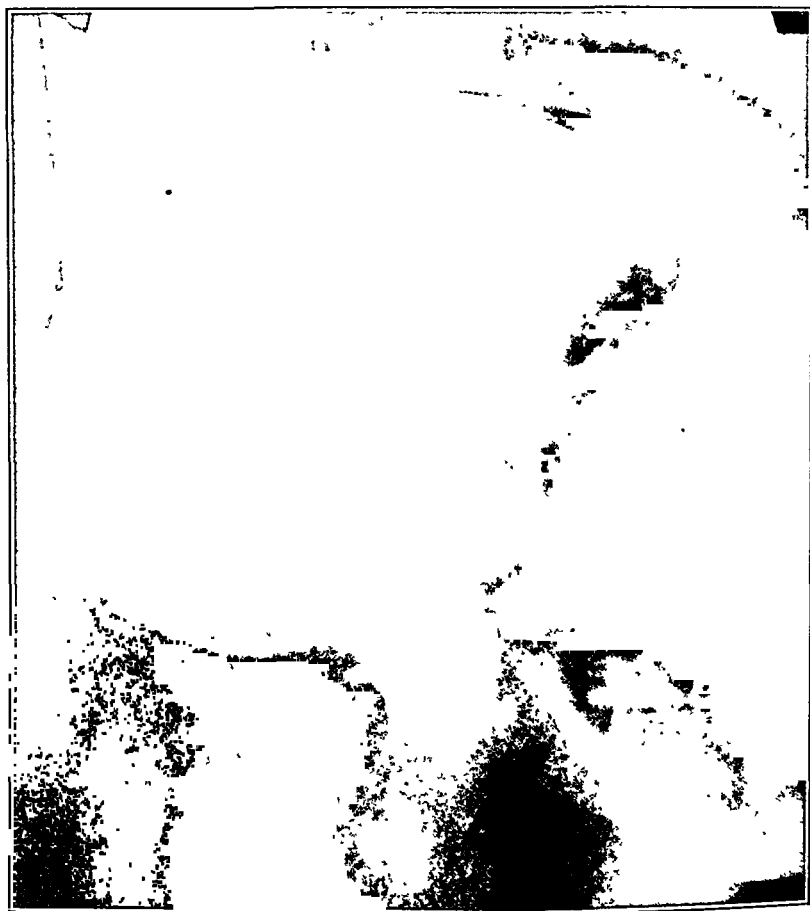


Case S 326. After onset

The *Barany test* was normal.

*Eye Examination* showed 20/60 vision in both eyes, yellow discs with indistinct margins, enlarged blind spots, normal form but contracted (left) color fields.

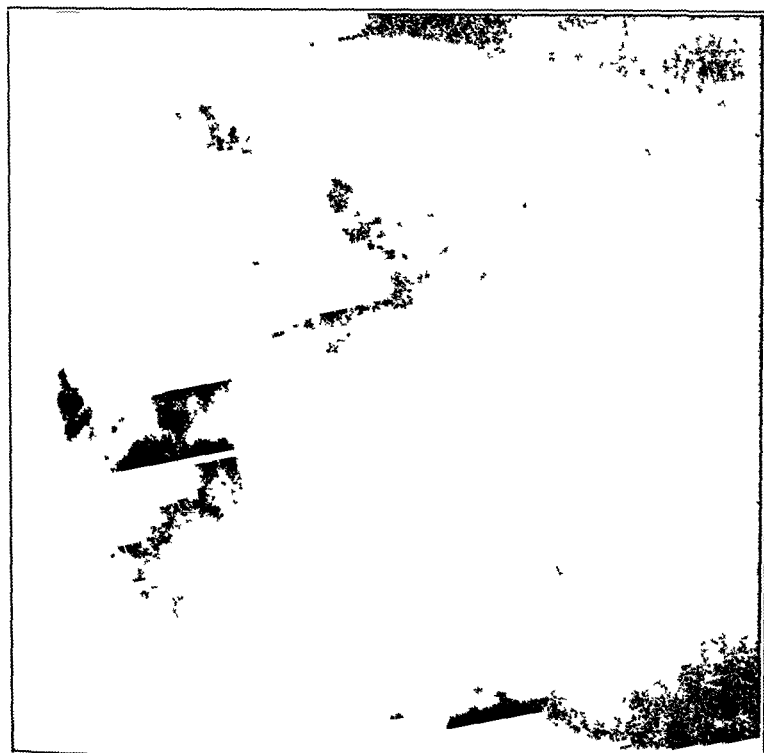
*Diagnosis:* From the picture presented the diagnosis was established as acromegaly with the gland in the final or hypo-functional state.



Case S-326. Before operation.

*Outcome:* As the patient was unable to work, he was retained at the hospital under observation. The condition seemed static, but in September there was a resumption of the headaches, which were very severe. After consultation it was decided to try the effect of deep x-ray irradiation, and on September 29 and October 7 treatments were given. These were followed by complete freedom from pain subsequent to the latter date. The color field showed marked improvement. Treatments were given on October 17 and 25 and November 7, there

having been but one slight headache in the interval. The patient desired to go home for Thanksgiving and was given a two-weeks' leave of absence. On his return in mid-December a laboratory check was started with the result that the first day's urine was found to be nearly eight liters and to contain 238 grams of sugar (see 326-a in Table XVII.) He was placed under active anti-diabetic treatment, the details of which are recorded elsewhere (54), and after showing a steadily rising blood sugar with massive insulin dosage, he rapidly returned to normal with full diet, no insulin, and disappearance of the glycosuria, hyperglycaemia, and polyuria. His laboratory picture in February, 1925, showed a mild bilobar overactivity, there being seemingly a recurrence of the earlier state. In June the headaches resumed; in July the anterior lobe had again become hypoactive, but the posterior overactivity had increased (see B-475). X-ray treat-



Case S 326 After operation

ments were resumed, but the headaches increased and in October the visual disturbances reappeared. By mid-November, however, the x-ray had again apparently controlled the situation. In a few weeks this was found not to be the case, and Dr W J Mixer was called in consultation. He advised operation, and through his courtesy the patient was transferred to his service at the Massachusetts General Hospital. Early in January, 1926, Dr Mixer performed a partial

trans-sphenoidal hypophysectomy, removing a considerable portion of the posterior lobe. Early in March the patient returned to us, having made an uneventful convalescence. Another study (B-475-a) showed a normal anterior, but apparently a still hyperactive posterior fragment. The hyperglycaemia and glycosuria were found to be present. Dr. Ulrich resumed contact with the patient and carried out a series of studies on the effect of insulin, already referred to. The patient is still under observation. There has been what seems to be a progressive upward trend to the functional activity of the anterior lobe, while the posterior fragment retains its overactivity. At the time of writing (April, 1928), the patient is having a fresh study, the results of which are not yet available. It may be said in passing that the possibility of other factors having entered the case has not been overlooked, though, as they are shortly to be considered fully, they need not be discussed here.

### CONCLUSION

A paper of this type cannot be briefly summarized. It may be stated that a long series of cases have been diagnosed on the basis of certain formulas established by extensive preliminary studies already discussed (1).

Specific glandular therapy administered in strict accordance with the diagnosis as established has been shown to be efficacious in a large number of patients, producing both an amelioration of the clinical symptoms and a complementary normalizing of those laboratory findings upon which, in part, the diagnosis was based.

It seems but fair to add that while the material for this presentation is drawn in largest part from earlier cases in the series, the later results confirm and substantiate in no uncertain manner the conclusions here offered.

It is impossible for the authors to render adequate thanks to the large group of colleagues and associates who have made such vital contributions to the studies here presented. To them is due a large part of the credit for whatever merit may be found in this work.

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# EFFECTS OF THYROXIN INJECTIONS ON THE SUPRARENAL GLANDS OF THE MOUSE

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## INTRODUCTION

The present investigation was undertaken to test the influence of an added amount of thyroid product on the histological structure of the mouse suprarenal. Beginning with the report of Magnus-Levy (1895), who first found that thyroid feeding may cause loss of weight in an animal, numerous papers have appeared recording an increase in body weight resulting from small dosage in thyroid feeding, and a decrease in body weight or a retardation in growth produced by higher dosages, the latter effect being possibly due, in the opinion of Hoskins (1916), to the toxic effect of the larger amounts.

Besides changes in body weight, other effects that have been reported include: (a) Interference with pregnancy by thyroid of probably toxic size (Gudernatsch, 1915), an effect similar to that observed by Stockard (1913) in animals treated with alcohol; (b) hypertrophy of certain organs, including the suprarenals, following thyroxin injections (Cameron and Carmichael, 1921); and (c) sex differences in the response of the suprarenals to thyroid feeding (Hoskins, 1916; Herring, 1917; Hewitt, 1920). A sex difference in the response of the suprarenals to gonadectomy has been reported by Hatai (1915).

On the histological side, Kolmer (1912) noted the degeneration and disappearance of the reticular zone of the guinea pig during pregnancy, while Masui and Tamura (1924), in a study of the reticular zone in mice, found that this disappeared in the male by forty days of age and in the female during pregnancy and old age. Further, after castration the cortex hypertrophied until it almost equaled that of the female in size, though no effect was observable following spaying. From this equalization of size of the suprarenals in gonadectomized animals the

authors conclude that "the zona reticularis is intimately related to the sex gland." Altenberger (1924) also reported hypertrophy of the cortex after castration in mice.

Tamura (1926) gives among the suprarenal changes observable in pregnancy in mice, the disappearance of the reticular zone and the hypertrophy of the zona glomerulosa, zona fasciculata and the medulla, with the appearance of a "zona gestationis" between the fascicular and reticular zones. This zona gestationis, he includes as part of the fascicular zone, though he says the cells cannot be distinguished from reticular cells in the non-pregnant animal.

In a description of the cortical zones of mice, Miller\* (1927) recognizes: (a) The glomerulosa, (b) the fasciculata, (c) a circular band of flattened cells crowded together in irregular arrangement and bordered by connective tissue externally, and (d) an "X zone" (the reticular zone of Tamura and others). According to Miller, the last mentioned disappears in the male by forty days of age, and in the female in the first half of the reproductive period, after which the gland in the female resembles that of the adult male. She also confirmed the absence of any effect on the reticular zone from ovariectomy, but emphasized the effect of pregnancy in hastening the disappearance of this zone.

In short, previous investigators have found that thyroid feeding and hyperthyroidism bring about changes in body weight of laboratory animals, and also an increase in the weight and size of the suprarenals. At the same time there is hypertrophy in the heart, liver and kidneys, organs more directly concerned in increased metabolism. Other abnormal conditions, castration, thyroidectomy, starvation, excision of the anterior pituitary, all of which involve unusual metabolic states, have likewise been found to cause an hypertrophy of the suprarenals. In the mouse, the reticular zone of the suprarenals disappears with age and sex development both of which are accompanied by changing metabolic rates. In the light of these several facts, it seemed to be a matter of considerable physiological interest to ascertain what changes might come about by increasing the amount of

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\* The present study was suggested by Mrs. Miller, and carried out under the direction of Dr. C. H. Danforth.

available thyroxin, which is known to stimulate metabolism markedly.

## MATERIALS AND METHODS

Mice, both male and female, were chosen as the experimental animals, and thyroxin, injected subcutaneously without anæsthesia, was employed as the means of supplementing the thyroid output.

Five groups of four males each, 32 or 33 days old, were selected, each group being composed of litter mates living in the same cage under identical conditions. The left suprarenal glands were removed, under ether anæsthesia, from two of each group to serve as controls in studying subsequent changes in the right glands.

For 21 days, the thyroxin was administered in the proportion of 1:10<sup>6</sup> by weight, following the method of Cameron and Carmichael (1921) with white rats. A drop of 2½ per cent NaOH was used to bring the thyroxin crystals into solution, and to this was added an amount of normal saline convenient for injection, the solution being made up each day just before use to avoid oxidative changes.

One of each pair of non-operated mice in each group was injected with thyroxin, and the other, which served as control, with an equal amount of normal saline and NaOH solution without thyroxin.

For the effects of injection on females, twelve nulliparous animals from 69 to 84 days of age, with the left suprarenals removed, were injected with the thyroxin over a period of 28 days. The dosage was the same for both males and females and was chosen in the hope that the metabolism would be sufficiently increased without obscuring the results by toxic effects. While the gain in body weight ranged from 10 per cent to 107 per cent in the treated animals, as compared with 23 per cent to 90 per cent in the controls, the dosage was apparently too toxic for four of them, the three smallest and one medium-sized mouse, for they died suddenly in the first ten days. However, death may have been due to other causes than hypersusceptibility to thyroxin, though nothing was disclosed at autopsy. Schafer (1924) reported that similar deaths had occurred during the experiments of other workers with thyroid secretion.

Since the gain in weight was constant and fairly marked in most of the mice, the dosage was doubled after the second week, with no fatalities and only one resultant loss in weight among the remaining twenty animals. In the third week signs of hyperirritability appeared, which were most noticeable during the weighing, when, instead of remaining quiet, as mice usually do during routine handling, some would jump restlessly up and down in the glass beaker in which each was weighed. This would seem to indicate that the dosage employed was about the maximum compatible with the purpose of the experiment.

At the end of the experimental period, the right suprarenals were removed under the same conditions as the left. The tissues were fixed in Mueller's solution, embedded by the chloroform-paraffin method, stained with Mayer's hematoxylin and counterstained with eosin, acid fuchsin or chromotrope.

To test the matter of a compensatory hypertrophy of one gland after the removal of the other, the left suprarenals of ten other males of 32 days of age were removed, and after the lapse of the experimental time, 21 days, the right glands were removed and the size of the two compared in serial sections. Both appeared to be of the same size.

According to Miller (1927) the left gland of mice is normally slightly larger than the right. Hence there seems to have been an hypertrophy sufficient to bring the size of the right up to that of the

EFFECTS OF THYROXIN INJECTIONS AFTER REMOVAL  
OF LEFT SUPRARENAL*A. Females (96 to 111 days of age at the close of the experiment).*

1. Size of glands. An increase of 70 per cent had occurred, as measured by a micrometer along the radius of a cross section. The greatest part of the increase was due to the expansion of the reticular zone. The medullary increase was 8 per cent, the reticular 100 per cent, and the fascicular 13 per cent (Fig. 1, B).

2. Zonal changes. On examining the cells in a given area by the use of a micrometer, the glomerular cells were found to be somewhat larger. The increase in this zone was due almost entirely to hyperplasia. The fasciculata cells were increased in number, but not in size. The intermediate zone of flattened cells showed an increase from the original 2-3 layers to 6-12 layers, and the cells were less flattened, rather polyhedral in outline, but irregular and crowded together, as if under considerable pressure, which gave them an appearance different from those in either of the neighboring zones. In many of the glands vacuolation started in this zone and in some cases was complete before much had started elsewhere, giving the appearance in section of a narrow, circular zone riddled with shot, as there was entire absorption of perceptible content with no confluence of cells. In the reticularis, great multiplication of cells had taken place, as shown by actual count, though the individual cells remained of the same size as before, with the exception of a few glands in which a relatively few degenerated cells, two or three in a group, had fused.

3. Denegeration. This, under ordinary conditions, would have progressed by 93 days of age to a maximum of vacuolation with fusion of neighboring cells and absorption (Miller, 1927). The effect of the thyroxin was to hold the stage of vacuolation almost stationary during the injection period of 28 days, and to result in an increase in the number of cells. Some of the glands had the "foamy" look mentioned by Masui and Tamura, which was regarded by them as due to liquefaction of secretory granules in the cytoplasm.

*B. Males (53-54 days of age at the close of the experiment).*

1. Size changes in male suprarenals after injections. Hypertrophy and hyperplasia of all cells occurred, with the exception of those of one gland which resembled that of the female after injection, i. e., with little hypertrophy accompanying the hyperplasia. Increase in cortex width was noticeable by micrometric measurement in every one of the fifteen, the least increase being 66 per cent, the greatest 200 per cent, and the average 109 per cent. Also, there was an increase in the number of rows of cells in the width of the cortex in every case, the greatest being from 0 to 34 cells, with an average increase in the others of 100 per cent. The increase in length of the whole gland was determined by counting the number of sections in comparable series, the average being 50 per cent. The width of the medulla had increased on the average 32 per cent, no decrease taking place in any part of the gland (Fig. 2 B).

2. Zone changes in the male glands. The cortex became similar to that of young, growing animals. In one-third of the glands the zone of cells between the fascicularis and reticularis was quite distinct, as in the females; in the others it was there, but less marked.

In the glands in which the reticular zone had entirely or practically disappeared before beginning the treatment, it had reappeared (Figs. 3, A and B). In all the others, not only had multiplication

of cells taken place in a given area, but the individual cells were larger, as if multiplication had not been sufficient to meet the new demands.

The glomerular cells were enlarged in all cases, except one in which the hyperplasia had been unusually great in all zones.

A distention of the blood vessels and increased size of cells showed in the medulla.

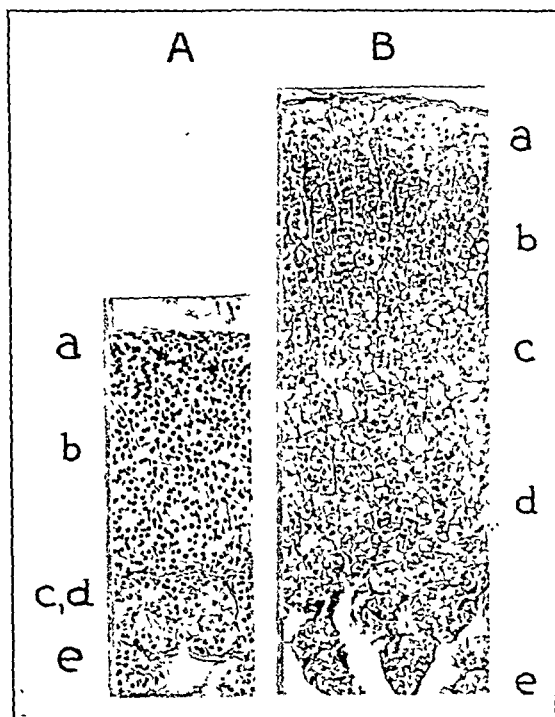


Figure 3. Suprarenals of a male. A shows only a remnant of the disappearing reticular zone. B, after thyroxine injection, shows the retention and hyperplasia of the reticular zone and subsequent degenerative changes.

3. Degeneration in the male glands. Though vacuolation does not occur normally during the disintegration of the reticular zone in the male (Miller, 1927), degenerative changes could be found in all of those injected, mostly just beyond the first stages of foamy structure and including also a few scattered vacuoles (Fig. 3, B). In several there was some absorption of contents and a little fusion of cells. In one, the vacuolation of the zone between the fascicular and reticular zones had progressed as in the females, showing the same small vacuolated cells.

#### THE EFFECT OF INJECTIONS ON MICE WITH BOTH SUPRARENAIS INTACT

In the controls the reticular zone had disappeared entirely as it does in all normal males over forty days of age, while in the others the thyroxine had caused not only a retention and increase of the

and pregnancy appear similar in kind if not in degree to those of hyperthyroidism.

According to Macleod (1927) the histological changes brought about in the suprarenal cortex by excision of the gonads are similar to those caused by thyroidectomy and by excision of the anterior lobe of the pituitary gland. It seems probable that the results of the experiments considered in this discussion, as well as the observations of clinicians, strengthen the assumption that there is an inter-relationship between the suprarenals, thyroid, gonads and pituitary in metabolism, and that a disturbance of the balance between them brings about a compensatory increase in the suprarenals lasting perhaps until a new balance is struck.

After thyroidectomy, the load carried by the thyroid in regulating metabolism is left for other organs, just as in hyperthyroidism the co-operation of the other organs concerned with metabolism is necessary for the adjustment of metabolic changes brought about by its hypertrophy. In castration, the enlargement of the thyroid and anterior pituitary as well as the suprarenals would seem to be a similar response. Since most observers agree that the suprarenals do not enlarge in pregnancy, it would seem as if nature had made other provision in the female for taking care of the additional demands in this case. It is known that the thyroid and anterior pituitary both hypertrophy during pregnancy, which seems consistent with the fact that spaying brings about no changes in the size of the suprarenals.

Applying this conception to the present study, we find that at the beginning of the experiment both sets of animals had reached a stage in growth when the rate of body metabolism was lessening, and degeneration of the reticular zone of the suprarenals was beginning. In the controls, this degeneration continued with complete disappearance of the reticular zone, which would seem to indicate that the normal metabolic burden incident to this age can be carried without these cells and that they hence degenerate. With the great increase of metabolism brought on by the thyroxin, those with both glands were able to meet the situation by doubling the amount of tissue in them, but during the experiment the rest of the body had so far adapted itself that degeneration in the reticularis could again set in. In the group



which had lost one gland by excision, the great increase in thyroxin threw a burden on the whole organism that had to be met at once, and could not be wholly cared for by the one remaining suprarenal. Before the end of the experiment, however, this adjustment had apparently been made successfully, for degeneration of the inner zone had progressed further in animals with only one suprarenal than in those that had both glands.

#### SUMMARY

1. The normal disappearance of the reticular zone in the male mouse after 40 days of age is confirmed.

2. Unilateral suprarenalectomy in the mouse results in dilatation of the vessels in the remaining gland, as measured in cross section, and a slight hypertrophy in 21 days.

3. (a) Daily thyroxin injections into unilaterally suprarenalectomized female mice, begun at about 70 days of age, bring about a marked hyperplasia in 28 days. The reticular zone becomes double in size.

(b) In the male, thyroxin injections begun at 32 days of age, under the same conditions, cause an increase in size and number of cells, the increase in size of cross sections being at least 40 per cent greater than that in the treated female, yet the male glands even then are smaller than those of the female.

4. The effects of thyroxin injections into male mice 32 days of age (no suprarenalectomy) stimulate a similar increase in both glands by 54 days of age, giving the non-suprarenalectomized animal twice as much cortical tissue as the suprarenalectomized and also twice that of the normal animal. A distention of blood vessels accompanies this increase.

5. A histological condition similar to that of the young, growing animal of both sexes, is produced in the male gland by injection of thyroxin. Where the normal disappearance of the reticular zone is completed, entire regeneration of the reticular zone takes place. A marked hyperemia and increased size of individual cells shows in the medulla.

In the female, all four zones have a part in the hyperplasia resulting from the injections.

6. The normal progress of degeneration of the reticular zone in the female was held almost in abeyance during the period of

treatment. Degeneration had begun in the suprarenals of all the thyroxin injected males, and had progressed least in the animals with both glands intact.

It is suggested that these glandular changes occur in response to the metabolic disturbances caused by the thyroxin, and that they are coincident with the establishment of the endocrine balance on a new level.

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# THE EFFECT OF X-RAYS ON THE ADRENAL GLANDS

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The effects of Roentgen rays on the adrenal gland as previously reported (Martin, Rogers and Fisher, 1924) are far from conclusive. Some destruction was produced but never to such a degree that one would expect symptoms of adrenal insufficiency to appear. In order to produce complete destruction of the adrenals it was decided to give larger doses and also to observe the animals for comparatively long periods of time following radiation. Stewart (1921) in his review of the literature stated that many of the conclusions regarding adrenal insufficiency were not warranted because of lack of proper evidence.

Incidentally, we thought it would be an excellent opportunity to observe the cholesterol of the blood. The relation of the adrenals to cholesterol metabolism has long been a matter of conjecture. After the removal of one gland Joelson and Shorr (1924) state that there is a hypercholesterolemia which is most marked two weeks after the operation. These investigators feel certain that there is a relationship between cholesterol metabolism and the suprarenals. The work of Randles and Knudson (1925) indicates that the adrenals do not produce cholesterol. Lucas (1926) found no appreciable change in the blood cholesterol following adrenalectomy.

## METHOD

The method of preparing the animals for radiation was essentially the same as that previously described (Martin, Rogers and Fisher, 1924). For these experiments we used a cylinder 6½ in. long and 2 in. wide, in order to exclude surrounding tissues as far as possible. After the cylinder was placed over the adrenal a careful examination was made to be sure that the

entire gland was included. Then the filter was inserted. The animals were kept under deep anesthesia. Ether was given every 4 to 10 minutes as indicated by the depth of respiration. At no time did any of the animals change position during the time of radiation. When the desired dose had been administered, the filter was removed and the adrenal examined to ascertain whether the relation of the adrenal to the cylinder had been changed. In no instance was there a change of position

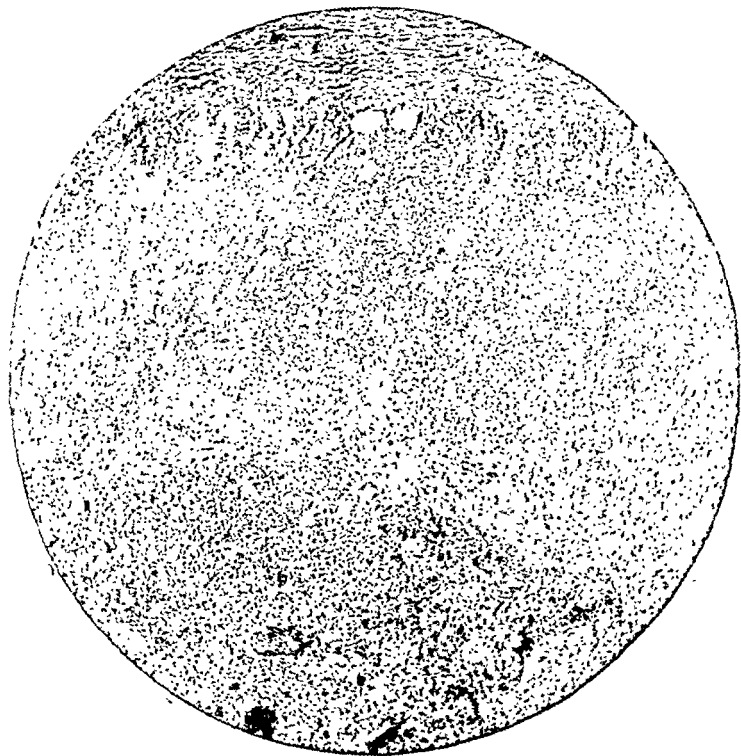


Normal adrenal of a dog. The three layers of the cortex and the well demarcated medulla with distinct blood vessels can be easily distinguished.

of the cylinder during radiation. The exposures were made by a 10-inch Standard X-Ray Transformer with a limited capacity setting. Under the treatment conditions of 140 KV., 5 MA., 2 mm. aluminum filter, 11-inch distance, the x-ray output was 65 R. per minute (40 R. of the German Bureau of Standards). About 6 minutes exposure represented a human erythema dose. By this method, the surface of the suprarenal gland received

390 R. primary rays. The secondary radiation was not measured, but on account of the size of the radiated region and the exposed object, this was evidently very little. The decrease of the intensity of the radiation within the object due to divergency and absorption is very limited on account of the thinness of the suprarenal gland and can be disregarded.

The right adrenal was removed from each of 4 dogs. After 2 to 5 weeks the left adrenal was given 3 to 5 erythema doses.



Adrenal of the dog exposed to five erythema doses. The thickening of capsule, the slight change of zona glomerulosa, the decided alteration of fasciculata with necrosis of cortical cells extending into the reticularis, and the medulla with thrombosed blood vessels are evident.

It was our purpose to observe these dogs for 6 months, at the end of which time a complete autopsy was to be performed and the glands studied microscopically. Three more dogs were selected to test the effects of x-rays at shorter intervals. In these three cases the preliminary operation of removing one adrenal was not performed. Four skin erythema doses were adminis-

The chief symptoms were very marked muscular weakness, anorexia and severe diarrhoea. The microscopic examination of the adrenal gland showed extensive destruction of the cells with marked fibrous tissue proliferation about the gland. There were, however, a few cells which appeared normal. The symptoms of this dog resembled very closely the clinical manifestations of Addison's disease. Microscopic examination reveals sufficient destruction to account for the symptoms. We realize that we cannot definitely state that this dog died from adrenal insufficiency, but the findings closely resemble the symptoms as described by Stewart and Rogoff (1925). Also we think it would be inadvisable to draw any definite conclusions based on the findings in one animal, but as we cannot continue this problem we feel that our results should be reported as a suggestive method for the production of Addison's disease. The method which we used seems to be satisfactory for producing a gradual destruction of the suprarenal tissue without apparent injury to any other tissues. Larger doses of x-rays would no doubt hasten the process and should be tried. It is only with the production of the condition experimentally that we can hope to study the therapeutic measures for its alleviation.

The changes in the cholesterol concentration of the blood are opposite to those of the other investigators cited. In three of the four cases in which the right adrenal had been removed, there was a slight decrease in the cholesterol, 21 to 41 days after the operation. After removal of one adrenal and radiation of the remaining gland, there were no significant changes even where there was marked destruction of the cortex. We do not feel that the changes which we observed during the course of these experiments show any relationship between the suprarenals and cholesterol metabolism.

### CONCLUSIONS

1. There appears to be no appreciable change in the blood cholesterol following the administration of 3 to 5 erythema doses to the left adrenal after the removal of the right adrenal.
2. The method described is suggested for the production of adrenal insufficiency in dogs.
3. The histological changes in the adrenals following radiation are in proportion to the number of doses administered.

We are indebted to Dr. A. J. Carlson for revision of the manuscript and to Dr. R. H. Jaffee for a study and description of the slides.

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# THE ADRENALIN CONTENT OF THE SUPRARENAL CAPSULE IN THE CHICK EMBRYO

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The time of appearance of adrenalin in the suprarenals has often been investigated. Fenger (1912) and McCord (1915) found adrenalin in the sixth week of embryonic life in cows, sheep and pigs. Miller (1926) found adrenalin and the chromic reaction in mice on the 14th and 15th days. Hogben and Crew (1923), using the intestinal assay method, came to the conclusion that adrenalin undoubtedly appears in chicks after the 16th day of embryonic development, but not before the 14th day. Lutz and Case (1925) also studied the chick embryo, using the frog's eye assay method. The presence of adrenalin was always demonstrated after the tenth day; in some, but not all cases it was found as early as the eighth day. As to human embryos, it was observed by Moore and Purinton (1900) and by Thomas (1926) that both adrenalin tests and the chromic reaction failed towards the end of embryonic development.

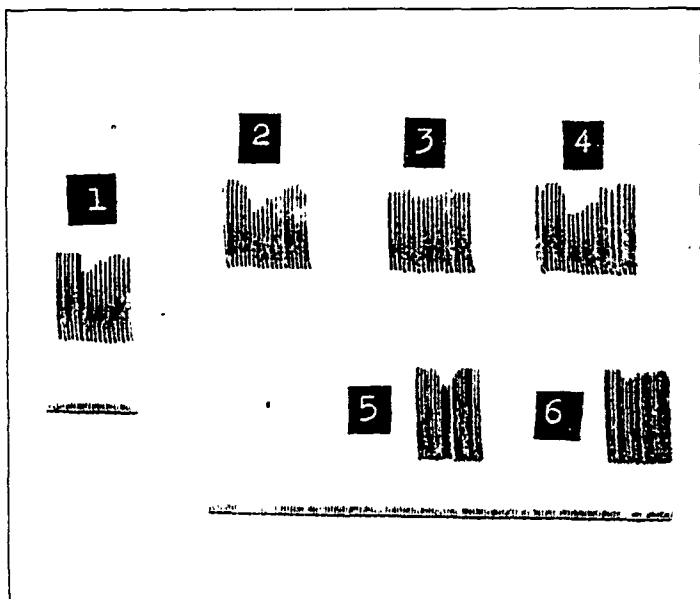
The present research with chick embryos was undertaken to determine the time when adrenalin appears, the relation between adrenalin and chromic reaction, and the increase of the former with the development of an embryo.

## MATERIALS AND METHODS

Eggs of Nagoya-cochin fowls were brought from a neighboring poultry farm one or two days after they were laid. Those of about the same size were selected and laid in an electric incubator of 38° C., and examined in succession at different periods of development. The methods for determining adrenalin are numerous, but each of them has its merits and demerits (Hoskins, 1911; Kodama, 1923). I adopted Cannon's intestinal method (Cannon and de la Paz, 1911). A piece of small intestine is suspended according to the method of Magnus in Ringer's solution (10 to 500 cc.), previously warmed. While the movements are being recorded on the smoked paper of a kymograph the emulsion of suprarenal capsule is flowed into Ringer's solution quietly along the wall of the receptacle. For the emulsion the suprarenal capsules are completely and quickly rubbed in a mortar, and then warm distilled water measuring about one one-hundredth of the



volume of the segment bath is added. The intestinal movement is depressed more or less in all cases. When it is restored to the previous condition, the Ringer's solution is first drawn off, and then the same volume of Ringer's solution of known adrenalin content is added. The same processes are repeated several times. Comparing each, one can easily appreciate the adrenalin content of the emulsion. (See the accompanying figure.)



1: the effect of emulsion of the suprarenal capsules obtained from an embryo of 11th day of incubation. 2, 3, 4, 5, 6: the effect of Ringer's solution containing 0.0006, 0.0002, 0.0007, 0.0005, 0.0004 mgm. of adrenaline, respectively. Time records, 6 seconds.

The points of especial importance in the manipulation are: (1) The temperature should be kept constant; (2) the supply of oxygen also constant and continuous; (3) the emulsion should be made as quickly as possible, and nearly in the same length of time; (4) the last dilution of the fluid should always be the same. From my own experience, the determination is done most favorably when the adrenalin content reaches approximately 0.005 mgm. dl. (5). The addition of emulsion of adrenalin should be conducted most carefully.

The chromic reaction was determined in the following manner: The suprarenal capsule is cut out with the surrounding tissues, fixed about five days in Orth's solution and imbedded in paraffin. The sections are stained with Giemsa or hematoxylin and examined under the microscope.

## EXPERIMENTAL RESULTS

1. *The appearance of adrenalin in the suprarenal capsules.* According to von Brunn (1872) and Lillie (1922) the cortex is founded on the fourth or sixth day of incubation and the medulla later than the eighth day. From my own experience it is impossible to separate the suprarenal capsules from other tissues until the sixth day of incubation because of its extreme softness and transparency. Even on the seventh day only scrupulous care leads to success. On and after the eighth day the manipulation grows easier as an embryo develops. With the seventh day embryo the intestinal proof failed in all cases. With the eighth day embryo and those of longer incubation positive results were secured and the increase of the reaction kept pace with the development of the embryo.

2. *The chromic reaction of cells of suprarenal capsules.* The reaction failed before the seventh day of incubation, on which day the medullary cells have not yet entered the cortical substance. On the eighth day one can observe for the first time medullary cells that react with chromic salts. On the ninth day and afterwards the staining as well as the number of cells showed an increment.

3. *The progress of development and the increase in the content of adrenal.* The examination began on the seventh day and continued until the 21st day of incubation. The first day means here the first 24 hours of incubation, and subsequent days each 24 hours, respectively. The 21st day begins at the end of the 20th day and lasts until three hours after the young chick makes itself a tiny hole on the shell with its bill. On and after the 12th day, the glands from each individual were large enough to be used. Before that time, five to ten, or even twenty, glands were rubbed together in a mortar, and the content of adrenalin pro rated. The term "adrenalin content" in the table stands for that extracted from both glands of one embryo. All the results may be summarized briefly in the following tables and curve:

## ADRENALIN CONTENT OF SUPRARENALS OF CHICKS

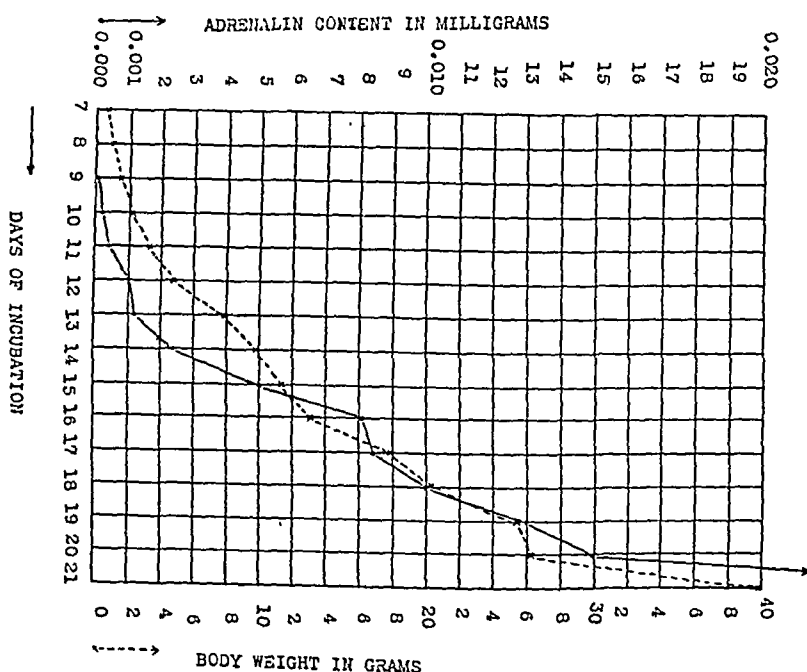
Average Body Weight Gms.	Adrenaline Content Mgm.	No. of Embryos Used	Volume of Solution Cc.
The 7th Day of Incubation			
0.70		10	10
0.68		20	10
0.67		20	10
0.68		20	10
0.69		20	10
Av. 0.68			
The 8th Day of Incubation			
1.01	trace	10	10
0.91	trace	20	10
0.98	trace	20	10
1.02	trace	10	10
1.01	trace	10	10
Av. 1.00	trace		
The 9th Day of Incubation less than			
1.45	0.0001	10	10
1.59	0.0001	10	10
1.50	0.0001	5	10
1.40	0.0001	5	10
1.52	0.0001	5	10
Av. 1.51	0.0001		
The 10th Day of Incubation			
2.38	0.0002	5	10
2.23	0.0002	5	10
2.28	0.0002	5	10
2.15	0.0002	5	10
2.25	0.0002	5	10
Av. 2.26	0.0002		
The 11th Day of Incubation			
3.26	0.0005	1	20
3.20	0.0004	1	20
3.20	0.0005	1	20
3.00	0.0003	1	20
3.40	0.0004	1	20
Av. 3.21	0.0004		
The 12th Day of Incubation			
4.8	0.0009	1	20
4.7	0.0009	1	20
4.8	0.0009	1	20
5.2	0.0012	1	20
4.6	0.0010	1	20
Av. 4.8	0.0010		
The 13th Day of Incubation			
8.32	0.0013	1	30
7.00	0.0010	1	30
8.80	0.0015	1	30
7.50	0.0012	1	30
7.05	0.0010	1	30
Av. 7.73	0.0012		

Average Body Weight Gms.	Adrenaline Content Mgm.	No. of Embryos Used	Volume of Solution Cc.
The 14th Day of Incubation			
9.2	0.0028	1	50
10.3	0.0022	1	50
9.2	0.0020	1	50
9.6	0.0020	1	50
10.5	0.0030	1	50
Av. 9.8	0.0024		
The 15th Day of Incubation			
10.75	0.0050	1	100
11.00	0.0050	1	100
11.50	0.0050	1	100
11.40	0.0050	1	100
12.00	0.0052	1	100
Av. 11.33	0.0050		
The 16th Day of Incubation			
14.0	0.0085	1	200
14.2	0.0085	1	200
12.5	0.0078	1	200
12.2	0.0078	1	200
12.0	0.0070	1	200
Av. 13.0	0.0081		
The 17th Day of Incubation			
18.2	0.0082	1	300
18.4	0.0086	1	300
17.0	0.0088	1	300
17.6	0.0081	1	300
18.1	0.0082	1	300
Av. 17.9	0.0084		
The 18th Day of Incubation			
20.2	0.010	1	300
20.8	0.010	1	300
21.5	0.011	1	300
19.4	0.010	1	300
19.2	0.010	1	300
Av. 20.2	0.010		
The 19th Day of Incubation			
25.8	0.013	1	300
26.1	0.014	1	300
25.5	0.012	1	300
25.0	0.012	1	300
26.0	0.013	1	300
Av. 25.7	0.013		
The 20th Day of Incubation			
26.0	0.013	1	400
26.5	0.017	1	400
26.4	0.014	1	400
26.4	0.015	1	400
26.5	0.016	1	400
Av. 26.3	0.015		
The 21th Day of Incubation			
39.6	0.039	1	500
40.0	0.038	1	500
39.0	0.039	1	500
40.7	0.042	1	500
40.0	0.040	1	500
Av. 39.8	0.039		

Emulsions of heart, liver, spleen, kidney, muscle, etc., were used as controls. Their corresponding quantity was taken at different periods of development and examined under respectively similar conditions. The results proved negative in nearly all cases. Only when they were used in great quantity was the intestinal movement sometimes checked.

### SUMMARY AND CONCLUSION

1. In the chick embryo the suprarenal adrenalin appears on about the eighth day of incubation, and chromic reaction of the gland cells sets in at nearly the same time. Their intimate relation, which Ogata (1916) pointed out, is thus confirmed.



2. The adrenalin content of the glands increases gradually with the progress of development in an incubator, but a more or less marked increment is found on the 13th to 14th, and the 20th to 21st days. It is interesting to note that this latter fact and Sendju's work (1925) on tyrosin during the chick's de-

velopment suggest a close relationship between tyrosin and adrenalin.

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## Book Reviews

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THE ENDOCRINE GLANDS AND AUTONOMIC SYSTEMS IN DEMENTIA  
PRAECOX. Gabriel Langfeldt, 1926. J. W. Eides Boktrykkeri  
A/S, Bergen Pp. 326.

This work represents perhaps the most searching investigation yet reported on the possible endocrine etiology of dementia praecox. The work was done at the Neevingaarden Mental Hospital at Bergen, Norway. Of the 320 patients available, 40 who were unmistakably diagnosed dementia praecox were selected. These comprised 16 who were clearly catatonic; 11, hebephrenic, and 13 mixed hebephrenic-catatonic.

In each case, in addition to the routine physical examination, careful observations were made on the size of the testes, size of the sella turcica, presence or absence of thymus shadow, condition of epiphyseal lines, blood morphology, basal metabolism, carbohydrate tolerance, presence of clinical signs of vagatonía and sympathicotónía and reactions to adrenalin, atropine, and pilocarpine.

Diffuse thyroid enlargement was found in 13 cases. No definite shrinkage of the testes, as was possibly anticipated, was found, but a marked preponderance in size and firmness in the hebephrenics as contrasted with the catatonics occurred. Lymphocytosis occurred in 7 of the 8 cases of acute catatonia, and in four of the mixed cases that were preponderantly catatonic. In only a single other case was lymphocytosis seen. The basal metabolism was low in 7 of the 8 cases of acute catatonia and in 4 mixed cases (catatonic); it was approximately normal in all but one of the rest of the 40 cases. In a few cases attempts to normalize the basal metabolism with gland products were unavailing. The results as regards glucose tolerance (from blood sugar curves) were not particularly convincing, but seem to show that there is a reduction during the acute phase of the disease. Glycosuria occurred notably more frequently in hebephrenia than in catatonia.

Both clinical and pharmacological findings support rather consistently the conclusion that in the catatonic group there is overactivity of both the sympathetic and parasympathetic nervous systems during the acute and stuporous stages: in the quiescent stage vagatonía alone is found. In hebephrenia, on the

contrary, the evidence points to sympatheticotonia throughout.

The author concludes that the results of this study definitely indicate that endocrine factors play an important role in the etiology of dementia praecox, but precisely what organs are at fault is still questionable. He ascribes a good deal of importance to "status thymicolymphaticus" in catatonia, but in view of the dubious endocrine standing of this "status" the conclusion is not illuminating.

Rather more convincing is the conclusion that the various phases of the manifestations of catatonia are to be explained as a result of a "struggle between the sympathetic and parasympathetic systems." In hebephrenia, on the other hand, the course of the disease is much less eventful because the sympathetic system is dominant throughout.

It cannot be said that Langfeldt has closed the subject—or, indeed, definitely settled any part of it—but he has placed on record a great many careful observations that must be taken into account in any subsequent research on the somatic phase of the dementia praecox problem.



# Abstract Department

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**Blood sedimentation in Addison's disease (La sedimentación globular en la enfermedad de Addison).** Bonilla, E. and A. Moya, Med. ibera, 511: 145-156. 1927.

The authors are making a systematic study of this sedimentation reaction in the endocrinopathies. From their studies in twenty-four cases of Addison's disease they believe that the Fähræus reaction has diagnostic value. An accelerated sedimentation time appears early in the disease and is a very constant finding. They believe that it has a certain prognostic value in that the graver are the manifestations of the disease the more rapid is the sedimentation.—G. M.

**Survival period in the pregnant and lactating cat following adrenal extirpation.** Corey, E. L., Proc. Soc. Exper. Biol. & Med. 25: 167-168. 1927.

The survival period of cats following complete adrenal extirpation was not found to be changed by pregnancy or lactation. These results are in contra-distinction to those reported by other workers for pregnant bitches.—M. O. L.

**Correspondence between the subperitoneal nervous plexus and the abdominal paraganglia (Zur Frage über die Wechselbeziehungen zwischen dem subperitonealen Geflecht und dem Paraganglion abdominale).** Dowgiallo, N. D., Ztschr. f. Anat. u. Entwicklungsgesch. 83: 598-604. 1927.

The work is based on a study of 46 dogs, 17 cats and 14 children, and is largely of morphological interest—A. T. R.

**Absence of fever in infected rats deprived of adrenal glands (Sur l'absence de fièvre dans l'infection du Rat privé de glandes surrénales).** Giaja, J., X. Chahovitch, and A. Giaja. Compt. rend. Acad. d. Sc. 184: 1680-1681. 1927.

Adrenalectomized rats, infected with a virulent strain of *B. pyocyneus*, show the same gradual fall of temperature as rats not so infected. Normal infected rats show a distinct rise of temperature of over 2°C. in the same period.—A. T. C.

**Adrenalin and muscle tonus (Über einen peripheren Angriffspunkt der Adrenalinwirkung auf den Muskeltonus).** Freudenberg, E. *Klin. Wchnschr.* 6: 634-635. 1927.

Following hyperventilation, muscle tetany has been shown to occur in skeletal muscle which has previously been injected with a solution containing novocaine, adrenalin and a potassium salt. Freudenberg reports the following experiment to show the role of adrenalin in the above type of tetany. During a preliminary three-hour period the person on whom the observations were to be made, took 10 g. potassium bicarbonate per os. Into the musculature of one thumb 0.0025 g. adrenalin was injected. Hyperventilation was begun immediately. The spasms which occurred in the injected thumb began sooner, were more intense and lasted longer than those which occurred in the uninjected thumb during and after hyperventilation. The experiment was repeated after 20 minutes with the same results. Identical results were also obtained the next day. The experiment furnishes no criterion as to whether the action is only peripheral or is both peripheral and central.

—M. W. Caskey.

**Embryology of the chromaffin system in man (Über die Ontogenese des chromaffinen Systems beim Menschen).** Iwanow, G., *Ztschr. f. Anat. u. Entwicklungsgesch.* 84: 238-260. 1927.

The study is based on 52 human fetuses from 5 to 290 mm. in length. Largely of morphological interest.—A. T. R.

**Topography of the paraganglia in man (Zur Frage der Topographie der Paraganglien beim Menschen).** Iwanow, G., *Ztschr. f. Anat. u. Entwicklungsgesch.* 84: 544-548. 1927.

A schema is given of the locations where paraganglia have been found, extending from the submaxillary gland to the lower portion of the abdominal cavity.—A. T. R.

**Hypoglycemia in scleroderma.** Longcope, W. T., *J. A. M. A.* 90: 1-7. 1928. *Abst., A. M. A.*

Eight cases of generalized scleroderma have been studied by the author with reference to the function of glands of internal secretion. In one case of generalized scleroderma with deep pigmentation, attacks of mental confusion and delirium occurred repeatedly after short periods of fasting. These attacks were associated with hypoglycemia. The resemblance between many of the symptoms in this case and those occurring in some instances of Addison's disease was noteworthy. In a study of five other cases of generalized scleroderma, the blood sugar, as well as the other chemical constituents of the blood, did not deviate materially from the normal. In three cases the basal metabolic rate tended to fall

below normal and the administration of thyroid extract in these cases was attended by symptomatic improvement. In one fatal instance of acute and extensive scleroderma in a young man, autopsy disclosed atrophy of one suprarenal gland and interstitial orchitis. Longcope suggests the possibility that disturbances in the function of the glands of internal secretion, which occasionally accompany scleroderma, may in some instances occur as a result of involvement of these organs by the generalized process, and thus do not have a direct bearing on the etiology of scleroderma.

**Toxic substances of the blood after extirpation of the adrenals** (Ueber toxische Substanzen des Blutes nach Exstirpation der Nebennieren). Putschkow, N. M., and A. W. Kibjakow, Arch. f. d. ges. Physiol. **218**: 83-88. 1927.

After adrenalectomy in dogs in certain cases death followed through paralysis of the heart. This was due to accumulation of choline in the blood, following a disturbance of the lipid transporting function of the liver.—A. T. C.

**Studies on cholesterol. III. The relation of the suprarenal gland and the spleen to cholesterol metabolism.** Randles, F. S. and A. Knudson, J. Biol. Chem. **76**: 89-93. 1928.

In 17 rats on a cholesterol-free diet removal of the adrenal glands had no effect upon the cholesterol content of the blood.  
—M. O. L.

**Sulfate retention in dogs following bilateral adrenal extirpation.** Swingle, W. W., and W. F. Wenner, Proc. Soc. Exper. Biol. & Med. **25**: 169-171. 1927.

Dogs with both adrenal glands removed and presenting marked symptoms of adrenal insufficiency showed a marked increase in the inorganic sulphate of the blood. This increase was most marked when the animal was verging on coma. Inorganic phosphate in the blood was also increased. The author believes that retention of the sulphate and phosphate ions plays a considerable rôle in the acid intoxication of adrenal insufficiency.—M. O. L.

**A biometrical study of the size inter-relationship of the glands of internal secretion.** Hammett, F. S., J. Metab. Research. **7-S**: 91-163. 1925-1926.

A biometrical study has been made of the weight inter-relations of the glands of internal secretion in a group of 121 males and 121 female albino rats 150 days of age of common inheritance and experience. The various organs show different degrees of association with the body weight and with each other.

Evidence is presented which indicates that in the albino rat up

to the time when the rate of growth becomes that of the mature adult, the physical well-being of the animal is more of a factor in the determination of the onset of thymic involution than is the age or physiological stage of development of the animal as a whole. This brings a new point of view to bear on the conception of this phenomenon. The only specific association exhibited by the thyroid is with the adrenals. This occurs in both sexes and is positive in direction. It supports the idea of a special functional inter-relationship between these two organs. The association is greater in the male than in the female. The adrenals are positively and specifically correlated with all of the other endocrine glands save the hypophysis in both sexes. The adrenal-pancreas association in the male is only a possibility. Analysis shows that the adrenals can be considered as a weak integrating mechanism binding together certain of the other incretory organs into an associative relationship. This influence is apparently more far-reaching in the female than in the male, and is attributable to the greater degree of association between adrenal weight and gonad weight in the former sex. It may mean that the adrenals are more important factors in the bodily economy of the female than they are in that of the male. The gonads show no particular predilection for specific weight correlation with any of the incretory organs save the adrenals. A weak positive correlation exists between ovary weight and hypophysis weight in the female, and a tendency toward weak negative ovary-thyroid and testis-thymus correlation seems to be present. The hypophysis is similarly unresponsive to weight changes in the other endocrine glands. In the female the gland shows only a weak positive correlation with the gonads. In the male a weak positive association with the pancreas is in evidence, and a possible weak negative correlation with the thymus. This situation is taken to indicate that the hypophysis either plays little special part in the activities of the other organs of internal secretion, or that it is largely uninfluenced by their variations. In the female the only specific association exhibited by the thymus is with the adrenals. This is positive in direction. In the male, on the other hand, a general, though weak tendency for weight association is present. This is definite, specific and positive with the pancreas and the adrenals. As with the thymus so with the pancreas, in the female the only specific association is with the adrenals, and this is only weakly positive. In the male, on the other hand, definitely specific though weak correlations are exhibited between the pancreas weight and the weight of the hypophysis and the thymus. There is the probability of a pancreas-adrenal association. These findings are not consistent with the idea that the glands of internal secretion are to be considered as a systemically specific functionally inter-related group in the normal organism. The organ of greatest variability in both sexes is the thyroid. The thymus is next in line. The adrenals,

gonads, hypophysis and pancreas fall into a group of definitely lower variability, which indicates a lesser sensitivity to the variability producing factors aside from those carried by the body weight and the other incretory organs.—Author's Abst.

**Cyclic changes in the ovary of the mole** (*Untersuchungen über das Ovarium von Talpa europaea mit besonderer Berücksichtigung seiner cyclischen Veränderungen*). Altmann, F., *Ztschr. f. Anat. u. Entwicklungsgesch.* 82: 482-569. 1927.

Serial sections of the ovaries of 98 specimens, representing every month of the year, were analysed by projecting them upon paper at various magnifications and then weighing the paper representing the various constituents. Of these animals, 31, were killed in March during the active sexual period and pregnancy. The interstitial cells decrease greatly during the active sexual period in the spring. This and the other elements in the ovary are discussed from the standpoint of their probable function.—A. T. R.

**Significance of pseudoepiphyses in endocrinology** (*Über die Pseudoepiphysen und deren Bedeutung in der Endocrinologie*). Rochlin, D. G., *Ztschr. f. Anat. u. Entwicklungsgesch.* 82: 354-367. 1927.

As a rule there is no epiphyseal ossification center on the distal end of the phalanges, first metacarpal and first metatarsal bones and on the proximal end of the second, third, fourth and fifth metacarpal and metatarsal bones. A more or less independent ossification center in any of above locations gives origin to what is termed a pseudoepiphysis. Pseudoepiphyses are most frequent in infantile retarded development and apparently where the endocrine disturbance is pluriglandular. Hypothyroidism seems to play a large role. Usually there is also hypogenitalism, but the sex glands are not considered to be a cause of the pseudoepiphyses. A pseudoepiphysis is especially frequent on the middle phalanx of the fifth finger. Bones with a pseudoepiphysis are usually too short. Pseudoepiphyses were not encountered in cases of excessive growth of bones in length nor in cases of accelerated differentiation, e.g., as in Basedow's disease and pubertas praecox. The report is based on 40 original cases with pseudoepiphysis, 32 of which were especially selected. The anomaly was present in 5.2 per cent of children from 2 months to 10 years of age.—A. T. R.

**Uterine and mammary development following injection of the ovarian hormone** (*Développement utérin et mammaire par injection d'hormone ovarienne*). Champy, C., and T. Keller, *Compt. rend. Acad. d. Sci.* 185: 302-304. 1927.

Continuous injections into castrated female guinea-pigs produce in 5 days phenomena comparable to those of the oestral pe-

riod, and in from 10 to 25 days uterine development comparable with that in pregnancy, with formation of decidual cells, a secondary mucous transformation of the vagina, and hypersecretion of its glands. Such injections into male guinea-pigs, whether castrated or not, produce similar marked development of the mammary glands to those produced in females, the maximum effects being produced in 15 to 18 days.—A. T. C.

**The variation in the unit of the oestrus-producing hormone.** Coward, Katherine H., and J. H. Burn, *J. Physiol.* **63**: 270-279. 1927.

An effort was made to obtain a more refined standardization of the hormone since it was found that a variation of 700% was sometimes found in the size of the dose of a given lot of the extract necessary to produce oestrus in ovariectomized rats. There was no correlation between body weight and the dose necessary to produce oestrus. Regeneration of ovarian tissue was found to have occurred in only 2% of rats and in 7% of mice. No significant differences were found between intraperitoneal and subcutaneous injections. Forty per cent of individual rats showed great irregularity in response to successive doses of the same size. The rat unit is "redefined as that amount of extract which produces oestrus in 50% of ovariectomized rats." The dosage for the mouse unit is the same as for the rat, although the latter averages 7.5 times the body weight of the former, so concentration in body fluids is not an important factor.—C. I. R.

**The effects of hysterectomy on the system of sex organs and on the periodicity of the sexual cycle in the guinea pig.** Loeb, L., *Am. J. Physiol.* **83**: 202-224. 1927.

Hysterectomy in the guinea pig, by prolonging the life and functional activity of the corpus luteum, interferes with the typical cyclic activity of the ovary and other reproductive organs and brings about the essential changes characteristic of pregnancy. These effects vary quantitatively according to the amount of uterus removed. How the operation causes these results is not clear. The similarity in the effects of hysterectomy and pregnancy on the corpus luteum suggests the possibility that a functional inactivity of the mucosa of the pregnant uterus is responsible for the prolonged functional activity of the corpus luteum.—E. P. Durrant.

**On ovarian hormones (Prüfung des Hormongehaltes von Corpus luteum präparation. XI. über weibliche Sexualhormone).** Loewe, S. and F. Lange, *Arch. f. exper. Path. u. Pharmakol.* **120**: 48-64. 1927. *Abst., Physiol. Absts.* **12**: 519.

The effect of ovarian preparations on the cycle of changes in vaginal smears of normal mice was studied. No activity was detected in agomensin, sistomensin, or luteoglandol.

**Creatinuria and castration.** Shen, T. C., *Chinese J. Physiol.* 1: 363-366. 1927.

The urinary creatine in dogs and albino rats was followed before and after castration. No demonstrable relationship was found between the male genital glands and creatine metabolism.—L. G. Kilborne.

**The Steinach operation (Die Ergebnisse der Steinach-Operationen).** Stettiner, H., *Deutsche med. Wchnschr.* 44: 1861-1863. 1927.

A review is given of German literature on the Steinach operation. The author contents himself with giving opinions of various authors without attempting to evaluate them or to arrive at any conclusion.—R. M. Oslund.

**Oestrus periods of rats in parabiosis (Über das Verhalten der Brunst bei der Parabiose der Ratten).** Zacherl, H., *Klin. Wchnschr.* 6: 1614-1615. 1927.

In nonpregnant rats joined together by colioanastomosis the authors observed that when the periods of heat did not fall together before the union, they never became synchronized afterward. The oestral cycles continued to be completely independent of one another. Pregnancy of the one did not prevent oestral cycles in the nonpregnant partner. When the parabiotic pair consisted of a male and a female, oestrus disappeared a few days after the union was made and did not return so long as they were united. Similarly when the junction was made between a female with normal oestral cycles and a castrated male or female there was cessation of oestral cycles.—C. P. Stone.

**A hormone of heart beat. VIII. Radiation experiments with fluorescent, ultraviolet, and Röntgen rays (Ueber ein Hormon der Herzbewegung. VIII. Bestrahlungsversuche mit Fluorescenz—Ultraviolett—und Röntgenlicht).** Haberlandt, L., *Arch. f. d. ges. Physiol.* 218: 129-136. 1927.

The active compound obtained in Ringer's solution from the frog's heart is partly but not completely decomposed by strong fluorescent and ultraviolet light. Aqueous extracts are largely decomposed by strong Röntgen radiation.—A. T. C.

**Influence of diuretics on pituitrin secretion (Untersuchungen über die Beeinflussung der Pituitrinsekretion durch Diuretica).** Hoff, H., and P. Wermer, *Klin. Wchnschr.* 6: 1180-1181. 1927. *Abst., Physiol. Absts.* 12: 512.

Diuresis was produced in dogs with euphyllin, novasurol, or urea, and cerebro-spinal fluid was withdrawn at intervals (from the cisterna magna) and tested for pituitary secretion by the virgin

guinea-pig uterus. Much more was present than before the diuresis. An opportunity to carry out the same test on a patient who underwent suboccipital puncture for diagnostic purposes showed also that, after euphyllin, there was an increased amount of pituitary secretion in the cerebro-spinal fluid. In three cases of idiopathic diabetes insipidus pituitrin was recognized in the suboccipital puncture fluid. The amount was not increased by euphyllin injection. It is concluded that diuresis stimulates the pituitary gland to secrete. Morphia and ether narcosis prevent this action, but chloretone does not affect it.

**The active principles of the posterior lobe of the pituitary gland. I.**

**The demonstration of the presence of two active principles. II.**

**The separation of the two principles and their concentration in the form of potent solid preparations. Kramm, O., T. B. Aldrich, I. W. Grote, L. W. Rowe and E. P. Bugbee, J. Am. Chem. Soc. 50: 573. 1928.**

The posterior lobe of the pituitary gland contains two important active principles: one which raises blood pressure and another which stimulates contraction of uterine muscle. A substantially complete separation of these two active principles has been accomplished by the employment of salting-out methods and, subsequently, by the use of appropriate solvents and precipitants. Solutions of these separated active principles have been recombined to form a pituitary extract identical with the original from which they were prepared, thus proving that no decomposition has taken place. The substantially pure pressor principle (beta-hypophamine) has been obtained in the form of a white, stable, water-soluble powder 80 times as potent as the International Standard Powdered Pituitary. The separated oxytocic principle (alpha-hypophamine) has been obtained in the form of a white, stable, water-soluble powder which is more than 150 times as potent as the International Standard Powdered Pituitary. The pressor principle has been shown to be responsible for the diuretic-antidiuretic action of pituitary extracts. The pressor principle when tested on animals for demonstration of pressor effects shows the development of tolerance which is characteristic of active pituitary extracts. It has been shown to possess no appreciable depressor action. Both active principles are basic bodies, presumably amines. Practical manufacturing methods have been developed for the separation of these two hormones and they have been made available to the medical profession for careful clinical trial. As a result of this preliminary work the foundation is now laid for an investigation of the chemical nature of the separated hormones of the posterior lobe of the pituitary gland, together with a more exhaustive study of their pharmacological properties.—Authors' Abst.



**Hypophysin and glycogenesis (Hypophysine et glyconéogénèse).**  
Nitzescu, I. I., and Marie Benetato, *Comp. rend, Soc. de Biol.* 98:  
58-60. 1928.

In rabbits, injection of posterior lobe extract causes an increase in glycogenesis in the liver and reduction, i. e. mobilization of muscle glycogen. This is true in both starving and well fed animals.  
—J. C. D.

**Changes in the hypophysis of the rat during pregnancy (Über die Veränderungen der Rattenhypophyse in der Gravidität).** Schenk, F., *Ztschr. f. Konstit.* 12: 703-711. 1926.

Twenty-five pregnant and numerous male and non-pregnant rats were investigated histologically. Pregnancy changes in the hypophysis of the rat are not as striking as in the human. The eosinophilic cells of the anterior lobe of pregnant rats stain less intensely and are less granular than in non-pregnant. The nuclei of these cells become less regular and the whole cell decreases in size. Other changes in the cytoplasm and nucleus indicate that many eosinophilic cells degenerate. Some of the chromophobes, or chief cells, seems to increase. Thus the sections stain with much less contrast. Six to eight weeks after littering some of these changes may still persist.—A. T. R.

**Dyspituitarism of the Lorain type, associated with a pituitary cyst arising from Rathke's cleft and secondary lesions in the hypothalamic region and ventricles.** Worster-Drought, C., W. C. C. Dickson, and B. W. C. Archer, *Brain*, 50: 704-718. 1927.

The condition described was present in a girl of 19, whose general appearance suggested a slender child of 6 or 7 (height 49 inches, weight 47 lbs.). No secondary sex characters had developed. The mental age was 13, and intelligence quotient 0.7. She died shortly after admission to hospital, death probably being caused or hastened by rupture of the cyst. The autopsy revealed the condition indicated in the title. If the pituitary possessed any function it could be but slight, since only remnants of both posterior and anterior lobes were present, as also of the hypothalamic region of the brain. This perhaps suggests that the Lorain type is apituitarism in contrast with dyspituitarism in the Frölich type.  
—A. T. C.

**The liver as the organ of sanguinification.** Adamson, J. D., *Canad. M. Ass. J.* 18: 147-150. 1928.

Equally good and parallel results were obtained in two cases of pernicious anemia placed on liver diet, and two to whom Collip's extract of liver was administered.—A. T. C.

**Changes in the eyeground in vascular diseases and in related conditions.** Altnow, H. O., Arch. Int. Med. 40: 757-785. 1927.

A study of twenty cases of thyroid disease with increased basal metabolism shows a rather striking absence of retinal arteriosclerosis when patients in the sixth decade are eliminated. In forty-seven diabetic patients of all ages (excluding children under 12 years) with and without hypertension, the incidence of definite retinal arteriosclerosis was 36.1 per cent in the latter and 81.8 per cent in the former. In both groups considered together, it was 42.5 per cent. These observations indicate that hypertension may play an important role in diabetes. The average age of diabetic patients with definite retinal arteriosclerosis was 57.7 years, while in patients showing doubtful or no retinal arteriosclerosis, the average age was 33 years. No patient under 30 years of age showed either definite or doubtful arteriosclerosis. If the presence of retinal arteriosclerosis is an index of sclerosis of the small vessels in other parts of the body (pancreas included), sclerosis of the small vessels may be an important factor in the production of diabetes after 50 years of age. Likewise, it does not appear to be a factor in the production of diabetes in the young person. Sclerosis of the choroidal vessels is more frequent in diabetes than in the other conditions studied. Changes in the disk are infrequent. If the ophthalmologist or internist sees eyegrounds exhibiting abnormally red retinas, numerous small round hemorrhages, groups of small yellowish-white and grayish-white spots on the central field of the retina, arteries with sclerotic changes, and well defined sclerosis of the choroidal vessel in the periphery of the retinal field with normal or nearly normal disks, in a person past middle life, he should strongly suspect diabetes.—From Author's Abst.

**Insulin and carbohydrate tolerance.** Brace, W. M., Ann. Int. Med. 1: 203-211. 1927.

Five selected cases of diabetes were placed on Newburgh and Marsh diets with just enough insulin to keep the urine sugar free. These patients received insulin daily for long periods of time, (32-45 months). From his results the author concludes that insulin is not capable of effecting a cure or a partial cure of human diabetes mellitus because the glucose tolerance was not increased.—E. L.

**Effect of glucose on the ketone body excretion in fasting depancreatized dogs.** Chaikoff, I. L. and J. J. Weber, Proc. Soc. Exper. Biol. & Med. 25: 212-213. 1927.

In completely depancreatized dogs, glucose administration was found to have no antiketogenic action.—M. O. L.

**The conservative treatment of gangrene complicating diabetes.** Harbinson, J. E., *Ann. Int. Med.* 1: 212-226. 1927.

A good review and discussion of the medical treatment of diabetic gangrene. An excellent bibliography is appended—E. L.

**Quantative and optimal action of insulin (Über die quantative und optimale Wirkung des Insulins).** Holm, K., *Arch. f. exper. Path. u. Pharmakol.* 121: 368-386. 1927.

It was previously shown that when the total subcutaneous dose of insulin was divided and injected at intervals the hypoglycemia appeared just as quickly but was stronger and more lasting than when the insulin was injected in one dose. The same observation was made with the continuous intravenous injection of insulin. The experiments in this paper deal with attempts to find the amounts of insulin required by a dog before and after depancreatization and with and without the administration of glucose. The insulin was given by the continuous intravenous method. The experiments were continued four weeks after extirpation. The weight of the animal decreased from 9.3 to 6.3 kgm. It was found that the normal dog maintains a normal blood sugar at an injection rate of 0.25 unit per hour. After depancreatization the insulin requirement is at first the same but gradually shrinks until not more than 0.065 unit per hour can be given without lowering the blood sugar. The author thinks that in a glycogen-rich animal the excess insulin may be "buffered" by the glycogen; there may also be an opposing action of adrenalin. The alimentary hyperglycemia produced in the dog, when sufficient insulin is continuously given to maintain a normal sugar level without food, differs from that in the intact animal. The fall in the curve is much slower and there is no subsequent hypoglycemia. This is because there is no endogenous source of insulin. Insulin and adrenalin secretions appear to be influenced in opposite directions by the amount of the blood sugar. If one covers the resting metabolism completely by the intravenous injection of glucose (in this case 3.5 grams per hour) then the insulin requirement is six times as great as in the fasting state, that is 0.4 unit per hour. The carbohydrate equivalent of insulin according to this experiment is 8.75 grams glucose per unit. A man weighing 60 kgm. would, therefore, require 7.8 units per day if he were fasting and without a pancreas, while he would require 48 units if his resting metabolism were covered by sugar. The author concludes that most of the experiments described in the literature dealing with the physiological effects of insulin really deal with its toxic action.—N. R. Blatherwick.

**Contributions on the action of insulin. II. Insulin-Adrenalin antagonism (Beiträge zur Wirkung des Insulins. II. Mitteilung: Insulin-Adrenalin-Antagonismus).** Issekutz, B. v., *Biochem. Ztschr.* 183: 283-297. 1927.

A perfusion apparatus for use with the livers of rabbits is described in detail. The author was able to determine simultaneously the rate of formation of sugar, acid and  $\text{CO}_2$ . The effects of adrenalin were an increase in the formation rate of sugar (if pH is below 7.5), and an increase in the formation rate of acid. The effect of insulin was a decrease in the rate of acid formation. A decrease in the rate of sugar formation could not be demonstrated, nor could a synthesis of glycogen. The decreased acid formation rate with insulin was explained tentatively on a basis of more rapid oxidation of the formed acids. In the presence of insulin, adrenalin failed to accelerate the rate of formation of either acid or sugar.

—B. S. Walker.

**Influence of nickel and of cobalt on the hypoglycaemic action of insulin in the rabbit** (*Influence du nickel et du cobalt sur l'action hypoglycémiant de l'insuline chez le lapin*). Labbé, M., H. Roubeau, and F. Nepveux, *Compt. rend. Acad. d. Sc.* 185: 1532-1534. 1928.

Nickel and cobalt salts augment and prolong insulin hypoglycaemia.—A. T. C.

**Action of nickel and cobalt salts on the hypoglycaemic power of insulin on the diabetic** (*Action des sels de nickel et de cobalt sur le pouvoir hypoglycémiant de l'insuline chez le diabétique*). Labbé, M., H. Roubeau, and F. Nepveux, *Compt. rend. Acad. d. Sc.* 186, 181-183. 1928.

Is observable in diabetic patients.—A. T. C.

**Case of insulin edema.** Leifer, A., *J. A. M. A.* 90: 610-611. 1928; *Abst., A. M. A.*

Leifer relates the case of a man who had diabetes and who developed a severe edema following the administration of insulin. Twenty-five units of insulin was given the first day. The next day, June 16, the patient already felt much better, and was given 30 units of insulin. June 17, 18, 19 and 20, he received 30 units of insulin daily but continued to have four plus dextrose in the urine and high blood dextrose, although he felt much better. His weight had already climbed to 141 pounds (64 Kg.). He was receiving a diet containing 750 calories at this time. No edema was visible. The carbohydrate in the diet was increased in greater proportion than was the protein or fat. June 21, 22 and 23, the patient received 50 units of insulin daily; on the 22d, pitting edema of the legs was first observed. The patient felt so well now that he insisted on going back to work but was not permitted to do so. The urine for the first time on the 24th contained no acetone, diacetic or betaoxybutyric acids, and only a trace of dextrose. On the 25th, his weight was 151 pounds (68.5 Kg.) and there was definite edema

of the lower extremities. The fluid intake was very slightly reduced but the salt intake was markedly reduced. Within ten days his weight came down to 139 pounds (63 Kg.) although his diet was gradually increased, and 40 units of insulin was being given daily. He has remained sugar free, feeling well and weighing between 137 and 140 pounds (62 and 63.5 Kg.). The edema is gone.

**The induced blood sugar curve found in muscular atrophy** (*La curva de glucemia provocada en la atrofia muscular*). Marañón, G., *Boll. d. Soc. Española de Biología*, 2: 43-59. 1926.

Marañón has made an investigation in five cases of muscular atrophy, determining the hyperglycemic curve by means of the determination of fasting glycemia at intervals of the half hour and hour following the injection of 25 grams of glucose in 200 cc. of water. He found the gradual curve of pre-diabetes in four cases. From these observations he concludes that the progressive muscular atrophy probably causes an unbalance of carbohydrate metabolism in the sensitive pre-diabetic. This alteration is regarded as due to depression of glucose consumption by the atrophic muscle. The other factors regulating carbohydrate metabolism doubtless compensate this muscular factor rapidly, hence glycosuria appears only in the pre-diabetic state. The intensity of the hyperglycemic reaction is correlated with the degree of muscular atrophy.—E. B.

**Acid base equilibrium in Addison's disease** (*El equilibrio ácido básico en la enfermedad de Addison*). Marañón, G., and M. Sarda, *Siglo méd.* 80: 197-199. 1927.

The acid base equilibrium has not hitherto been studied in Addison's disease. In six cases the authors found four in which there was a manifest decrease in the alkaline reserve and in the two others a tendency to this condition. There appeared to be a definite relationship between the degree of alkaline depletion and the intensity of the general picture. The authors surmise that the comatose termination of Addison's disease may be due to acidosis. The observations suggest the desirability of alkaline therapy in Addison's disease, especially in the advanced forms when acidosis is manifest. Insulin, which is too often used in different forms of acidosis should not be employed in Addison's disease on account of the marked susceptibility to this hormone unless large quantities of glucose are previously given.—E. B.

**A case of chronic glycosuria, probably of extra-pancreatic etiology.** Mason, E. H., and R. A. Flack, *Canad. M. A. J.* 17: 1294-1299. 1927.

A woman, following pregnancy in 1916, exhibited almost constant slight glycosuria but without symptoms of diabetes mellitus,

and with a renal threshold of 0.07% glucose and normal fasting blood sugar. After administration of 100 grams glucose by mouth blood sugar rose to 0.185% and there was appreciable delay in its decline. During following years there was no restriction in diet. Eight tests made during a second pregnancy in 1921-2 showed glycosuria on only one occasion. Subsequently glycosuria has been constant. Re-examination in 1927 showed fasting blood sugar over 0.15%. After two days on low carbohydrate diet it fell to 0.10%. Renal threshold for glucose was now 0.14% and after 100 grams glucose by mouth blood glucose rose to 0.37% in two hours and fell slowly. Respiratory studies indicated that there was present no marked impairment of glycogen storage, nor of glucose oxidation, suggesting that this case does not accord with the fundamental conception of true diabetes mellitus. The authors suggest that there is present a hyperactive sympathetic nerve supply to the liver, maintaining an excessive rate of glycogenolysis of liver glycogen, independent of any pancreatic disturbance.—A. T. C.

**Diabetes among the Chinese: Danger of insulin usage.** Mills, C. A., *China M. J.* 41: 914-921. 1927.

The author points out that insulin should be used with particular caution in Chinese since they appear to be hypersensitive to it. Of 22 Chinese diabetics treated with insulin three died in insulin shock, one died two days after a severe insulin reaction and two others had severe reactions from which they recovered. The hypoglycemic reactions, when they occurred, were very severe and protracted, and a large amount of glucose was required to secure recovery. As a rule, however, diabetes among the Chinese tends to be mild in type, and in most instances is accompanied in its onset by acute purulent infections. Calculated on the basis of hospital statistics diabetes is almost four times as frequent among Chinese males as among females.—L. G. Kilborne.

**Rapidity of sedimentation of red blood cells in human diabetes** (*Vitesse de sédimentation des globules rouges dans le diabète humain*). Nitzescu, I. I., and J. Gavrilă, *Compt. rend. Soc. de Biol.* 98: 63-64. 1928.

The red cells, as tested by the authors' method, settle more rapidly in diabetics (32 cases) than in normal humans. The more severe the condition, the more rapid the settling. This is but slightly modified by insulin treatment and is not dependent on the amount of blood cholesterol.—J. C. D.

**The injection of insulin and thyroid in large doses in the cachexia of nurslings** (*Las inyecciones de insulina y de extracto tiroideo a altas dosis en las caquexias de los lactantes*). Nobecourt and Levy, *Progresos de la clínica*, 179: 523-535. 1926.

The authors recommend the treatment of these cachexia states by the injection of insulin (3, 4 or 5 units per kgm. body weight) daily in single or divided doses immediately before giving the sweetened beverage. The injection is preceded by 10 to 40 cc. of glucose serum in order to prevent possible accidents. The treatment is carried on 10-15 days and can be repeated if necessary. The injection of liquid thyroid extract is also useful in the cachexia states. This may be employed in concentration of 10 centigrams per cc. administered in doses varying from 0.25 to 0.1 grams. The increase of weight obtained by this treatment is believed to be due to fixation of water by the tissues, but a possible trophic action of these products is not excluded.—E. B.

**Insulin and the mortality rate from diabetes mellitus.** Rabinowitch, I. M., *Canad. M. J.* 17: 1415-1424. 1927.

Rabinowitch has made a careful statistical study of the data available from the diabetic clinic of the Montreal General Hospital from 1921 to 1927 inclusive. The results show definitely that the use of insulin has produced a lowering of the mortality rates. During the same period diabetes mortality statistics for many large cities and districts in America and Europe do not show a decrease, and some show an increase. The cause of this apparent discrepancy is discussed, and it is considered due to insufficient diet-insulin control.—A. T.

**Lowering of blood sugar through parasympathetic stimulation** (*Experimentelle Beiträge zur Wirkung der Parasympathikusgifte auf den Blutsucker. IV. Fortsetzung der Untersuchungen über Herabsetzung des Blutsuckers durch Parasympathikesreizung*). Sakurai, T., *J. Biochem.* 8: 365-370. 1928.

By the use of selective parasympathetic stimulants, ergotoxin and pilocarpine, the blood sugar of rabbits was lowered.—M. O. L.

**The effect of glucose on ketosis.** Selle, W. A., *Proc. Soc. Exper. Biol. & Med.* 25: 219-221. 1927.

In four completely depancreatized dogs the administration of glucose by mouth or hypodermically, failed to diminish the ketone bodies of the urine. In two cases an increase was observed in the acetoacetic acid during the experiment. In one case, hydroxybutyric acid also was increased.—M. O. L.

**The hypoglucaemic properties of galegine sulphate** (*Sur les propriétés hypoglycémiantes du sulfate de galéguine*). Simonnet, H. and G. Tanret, *Compt. rend. Acad. d. Sc.* 185: 1616-1617. 1927.

In the normal dog and man administration of galegine sulphate may produce a fall of sugar exceeding 20%.—A. T. C.

The glycemie curve in states of prediabetes (*Las curvas de glucemia en los estados prediabéticos*). Soler, B., *Ann. Acad. Medico Quirurgica Española*, 6: 382-393. 1927.

Utilizing Marañón's technic, Soler studied the glycemie curve in various dermatoses (psoriasis, erythema, syphilis, varicose ulcers, recurrent erysipelas, ferunculosis, etc.). He frequently found the pre-diabetic curve. He regards the recognition of this state as important in its relation to treatment.—E. B.

Is insulin inactivated by glucose? du Vigneaud, V., *J. Biol. Chem.* 73: 275-283. 1927.

Twenty-two separate experiments were run in the attempt to demonstrate an inactivation of insulin by glucose, using on an average five rabbits for each experiment. The decrease in blood sugar obtained in the test animal was often slightly less than that in the control. The difference, however, was not great enough to be interpreted as indicating definitely an inactivation, in view of the great variability in the response of rabbits to insulin. In certain experiments where it appeared that inactivation had resulted, the use of more rabbits negated the difference between control and test. The average decrease in blood sugar of 60 tests was 41.8 mgm. per 100 cc. of blood; the average of 44 controls as 45.1.

—Author's Abst.

The sulfur of insulin. du Vigneaud, V., *J. Biol. Chem.* 75: 393-405. 1927.

If the active principle itself actually contains sulfur, as there is good reason to hold, then it is believed that the evidence presented in this study indicates that this sulfur is present as the disulfide linkage and that insulin is most likely a derivative of cystine. By means of the phosphotungstic reaction it was found that as the insulin became more purified the cystine content increased. The proportionality was so striking that it has given hope that this might prove to be a suitable means of assay for purified preparations. When the sulfur was split out, the disulfide linkage was destroyed and the test for cystine greatly reduced in intensity, indicating this as the source of the labile sulfur. Since it has been shown that insulin itself does not give the specific Sullivan reaction for cystine, and since the presence of cystine in the hydrolyzed insulin preparations has been demonstrated, it must be concluded that the cystine is present as some derivative. The behavior of the sulfur in insulin is quite parallel to the behavior of the sulfur in amino acid derivatives of cystine and suggests that the cystine in insulin is linked to the rest of the molecule by a peptide linkage. In this connection the high arginine, histidine, and tyrosine contents of purified preparations might be recalled. In Abel's analy-



ses the calculated empirical formula of  $C_{45}H_{73}O_{17}N_{11}S$  is based upon the presence of 1 sulfur atom in the molecule. From this work on the presence of the disulfide linkage the minimum value would have to be twice that given, or  $C_{90}H_{150}O_{34}N_{22}S_2$ .—Author's Abst.

Cause of increase of insulin in the blood of pancreatic vein following intravenous injection of synthaline (Sur les causes de l'augmentation de la teneur en insuline du sang veineux pancréatique après l'injection intraveineuse de décaméthylènediguanidine). Zunz, E., and J. LaBarre, *Compt. rend. Soc. de Biol.* **97**: 1801-1802. 1927.

As shown by studies on dogs, this condition depends on stimuli received through the vagi.—J. C. D.

The effect of hypercalcemia on the creatin output in myasthenia gravis. Berglund, H., Grace Medes and Anne Lohmann, *Proc. Soc. Exper. Biol. & Med.* **25**: 204-205. 1927.

In a patient with myasthenia gravis and creatinuria, fed on a creatine-free diet, the blood calcium was caused to rise from 10.6 to 13.3 mgm. per 100 cc. by the administration of parathyroid hormone and calcium lactate. No changes were found in the excretion of creatine.—M. O. L.

Do blood and serum contain some protective agency against the sequelae of parathyroidectomy? (Enthalten Blut und Serum einen Schutzstoff gegen die Folgen der Parathyroidektomie?) Greenwald, I., *Arch. f. d. ges. Physiol.* **218**: 169-175. 1927.

Theoretical and experimental evidence is adduced against this view.—A. T. C.

The standardization of parathyroid activity. Hanson, A.M., *J. Am. M. Ass.* **90**: 747-748. 1928.

Use is made of the fact that relatively small doses of the parathyroid hormone will restore parathyreoprivic dogs to normal. The reaction is more uniform than the hypercalcemia of normal animals. Parathyroid extract, for clinical use, should be standardized against a known hypocalcemia. The use of a smaller, accurately standardized unit avoids the danger of inducing a marked hypercalcemia.  
—R. G. H.

Treatment of tetany and spasmophilia in adults by bone transplantation. Krinicki, J. M., *Arch. f. klin. Chir.* **147**: 530. 1927. Abst. *J. A. M. A.* **90**: 66.

In a previous communication the author showed that a state of hypercalcemia can be produced in a guinea-pig by means of bone

transplantation. The experiment was later applied to human beings afflicted with surgical conditions associated with spasmophilia or tetany. This resulted in a rapid disappearance of spasmophilic symptoms and an associated rise in the blood calcium level. Heterogenous transplants proved to be just as efficient as homogenous. Ordinary soup bone may be used. He transplanted a piece of bone measuring about 5 cm. by 3.4 cm. by 0.5 cm. into the subcutaneous tissues. In his opinion, the result obtained cannot be explained on the basis of the transplant acting as a depot of calcium. One is lead to believe that some hitherto unexplained reciprocal action between the transplant, the parathyroid hormone, the blood and the tissues takes place.

**The use of parathormone in the treatment of infantile tetany.**  
Leitch, D. B., *Canad. M. A. J.* **17**: 1321-1323. 1927.

In a series of seven cases of infantile tetany parathormone (Lilly) was injected subcutaneously, 40 units a day, without any other medication. There followed rapid disappearance of symptoms of tetany, accompanied by increase of blood calcium, indicating that the internal secretion is in itself effective, though it is considered that the usual treatment should include in addition administration of calcium lactate and cod liver oil.—A. T. C.

**The effect of CO<sub>2</sub> administration upon parathyroid tetany.** Swingle, W. W., W. F. Wenner and P. Stanley, *Proc. Soc. Exper. Biol. & Med.* **25**: 165-167. 1927.

In dogs suffering from tetany experimentally induced by parathyroidectomy, the symptoms were markedly relieved by CO<sub>2</sub> administration. This relief lasted for several hours, and the effect could be repeated. The serum calcium level was not changed but the blood lactic acid was increased from about 27.5 mgm. to 100 mgm. per 100 cc. following CO<sub>2</sub> treatment.—M. O. L.

**Pineal pathology.** Horrax, G. and P. Bailey, *Arch. Neurol. & Psychiat.* **19**: 394-414. 1928.

Horrax and Bailey present three case studies as evidence on the pineal problem. The first, that of a boy of 9, showed slight pubertas praecox, with spermatozoa formation and a large pinealoma. Whether the tumor was productive or destructive is not clear. In a second case a man of forty was found to have normal mental and physical development with the pineal entirely replaced by a ganglioneuroma. The third patient was sexually mature at the age of three. He had a large tumor of the third ventricle but a normal pineal body. The thyroid, adrenals and hypophysis were also normal, according to autopsy study.—R. G. H.

The clinical and experimental studies on the effect of quinin upon the nitrogen metabolism of hyperthyroidism. Aoki, K., *Folia Endocrinol. Japonica*, 3: 47-49. 1928.

In three dogs the feeding of desiccated thyroid gland substance caused an increase in total nitrogen, ammonia and creatin-nitrogen. Urea nitrogen was decreased and the ratio of creatinin to total nitrogen was not changed. When quinin muriate was administered with thyroid gland substance the changes in the nitrogen partitions were less marked.—M. O. L.

The thyroid in infections and toxemias. Cole, W. H., and N. A. Womack, *Proc. Soc. Exper. Biol. & Med.* 25: 188-191. 1927.

In 7 dogs which succumbed to peritonitis, pneumonia and such severe infections, the iodine content of the thyroid was compared to that of 7 control dogs of equal weight which were kept and fed under the same circumstances as the dogs which died from infection. Analyses revealed 0.147 mgm. iodine per kgm. of body weight in the thyroids of the dogs with infection and 0.382 mgm. per kgm. body weight in the thyroids of the healthy control dogs. The weights of the thyroids, however, varied in a reverse manner. There was 0.294 grams thyroid tissue per kgm. of body weight in the dogs with infection, whereas the healthy control animals had only 0.191 grams thyroid tissue per kgm. of body weight.—M. O. L.

Nephrosis of thyroid origin. Davidson, J. R., *Canad. M. A. J.* 18: 161-164. 1928.

An uncomplicated case of thyroid nephrosis of many years' standing was materially improved by thyroid treatment. A second case, recently developed following influenza, did not respond to thyroid treatment until in addition injections of Collip's parathyroid extract were given, when marked clinical improvement followed, coincident with return of basal metabolic rate to normal. Subsequently the patient was controlled satisfactorily with thyroid alone. In a third case, following a series of unsuccessful pregnancies, in the second month of pregnancy, a definite nephrosis accompanied by a basal metabolic rate of minus 12% was successfully treated with thyroid. It is suggested that cases of nephrosis in which albuminuria precedes oedema by a period of months or years respond more readily to thyroid treatment than when oedema accompanies or immediately follows the albuminuria.—A. T. C.

Preoperative use of compound solution of iodine in exophthalmic goiter. DeCourcy, J. L., *Ann. Surg.* 86: 871. 1927.

It is now fully established that the pre-operative administration of Lugol's solution to patients with exophthalmic goitre lowers the

basal metabolic rate, controls the toxic symptoms, and lessens the hazards of operation. When the patient has been treated with a preliminary course of compound iodine solution, the thyroid gland at operation is found to be oedematous, so that the gland when sectioned exudes a very watery liquid. This condition is not true of hyperplastic thyroids not treated previously with Lugol's solution nor of ordinary colloid goitre. From this constant observation, the author thinks that the beneficial effects of iodine are brought about by a rapid formation of colloid material in a gland famished for iodine, resulting in back pressure not only on the cells and acini, but also on the thin walled veins surrounding the acini. In the opinion of DeCourcy, this back pressure causes the passive edema.

The swollen condition of the acini renders the secreting cells temporarily inactive, this effectively preventing the absorption of the toxic substance. In course of time however, new blood vessels are formed and the older ones gradually accommodate themselves to the changed condition. The patients once again become toxic with the absorption, even though the colloid formation may still persist in the gland. This explanation would account for the fact that improvement from iodine medication is only temporary.

—Author's Abst.

**End-results from the surgical treatment of hyperthyroidism.** Frazier, C. H., and W. B. Mosser, J. Am. M. Ass. 90: 657-659. 1928.

A careful follow-up study on 146 patients who have undergone subtotal thyroidectomy leads the authors to conclude that operative treatment of hyperthyroidism offers a chance for recovery from thyrotoxicosis in about 96% of cases. Complete restitution can be expected in 75% of cases. About 15% will have mild residual symptoms. About 5% will be permanently handicapped. About 3 or 4% will have recurrences. The degree of disability is proportional to the duration of the disease. Early operation will prevent the occurrence of permanent disability.—R. G. H.

**Influence of disease of thyroid on menstruation.** Gardiner-Hill, H., and J. F. Smith, J. Obst. & Gynec. of Brit. Emp. 34: 701. 1927; Abst., J. Am. M. Ass. 90: 806.

An examination made by Gardiner-Hill and Smith of 300 cases of thyroid disease showed that menstruation may or may not be affected in these conditions, but when it is, the alteration tends to be in a uniform direction. The type of menstruation varies inversely with the degree of thyroid activity, i. e., in hypothyroidism there is often a tendency to excessive hemorrhage and in hyperthyroidism, to amenorrhea.

Certain advantages of total thyroidectomy in selected cases of thyrotoxicosis of the exophthalmic type. Gilman, P. K., and W. E. Kay, *Am. J. M. Sc.* 175: 350-360. 1928.

From the results of several years observation of thyrotoxic patients by the ordinary surgical means the authors were led to feel that the return to health of many of these patients was incomplete—also that many of them relapsed in spite of good medical care. It appeared that the less of the gland that was left, the better was the ultimate result and the less was the likelihood of a relapse; also the less was the post-operative mortality, the shorter the convalescence and the sooner were the patients able to resume their occupation. It was decided to subject 22 patients to a complete thyroidectomy. Their cases are reported. It was found that the conclusions above mentioned were fully substantiated. Thyroid substance had to be administered, of course, but the regulation of this by basal metabolic determinations was not difficult. Several of the patients were able to determine subjectively the amount of thyroid substance required. Even in the seemingly hopeless cases the results of total thyroidectomy were most gratifying. The patients after long periods of invalidism have resumed their usual occupation and enjoy good health.—R. G. H.

X-ray treatment of goiter. Grier, G. W., *Ann. Int. Med.* 1: 241-246. 1927.

This is a clinical paper with no bibliography included. The author believes that radiation can be used successfully in hyperthyroidism if there is no malignancy of the thyroid, or in an inoperable intrathoracic thyroid. He also thinks that hyperthyroidism is a response to toxemia as a large number of his cases had pathological tonsils or infected teeth. Rest, fresh air, good food and sleep are essential to recovery. About six months are required for treatment. With the x-rays one-half an erythema dose is applied to one lobe of the thyroid each week. After two treatments the patient is allowed to rest for two weeks before continuing. When radium is used half an erythema dose of gamma radiation is applied and then repeated in six or eight weeks if necessary. The author prefers the x-rays to radium. A lowering of the pulse rate and a decrease in nervousness is usually noted in a month. Basal metabolism tests should be made and when the rate reaches plus ten or thereabouts the treatments should be discontinued before the thyroid reaches the normal level or the cumulative effect of the radiation may induce hypothyroidism.—E. L.

Studies on the heart in thyroid disease. 1. Changes in the T wave of the human electrocardiogram following iodine medication and thyroidectomy. Hamburger, W. W., M. W. Lev, W. S. Priest, and H. C. Howard, *Tr. A. Am. Physicians*, 42: 22. 1927.

Iodin medication (Lugol's solution) in hyperthyroidism results in most instances in diminution of the height of the T wave of the human electrocardiogram. Subtotal thyroidectomy is followed by an even greater decrease in the height of the T, in 3 cases progressing to inversion. Following iodine medication and thyroidectomy the decrease in basal metabolic rate parallels the decrease in height of T. Inversion of T following thyroidectomy occurs as a delayed inversion, in contrast to the immediate inversion from digitalis and the dove-shaped inversion of coronary occlusion.—I. B.

**Basal metabolism in organic heart disease.** Hamburger, W. W., and M. W. Lev, *Tr. A. Am. Physicians*, 40: 159-161. 1925.

Seventy-five per cent of cases of organic heart disease with decompensation show an increased basal metabolic rate of an average of 39% above normal. The rise in metabolic rate is in proportion with the degree of decompensation and the cardiac and respiratory rate. In a case of paroxysmal tachycardia the basal metabolic rate increased 11.1% during the paroxysm. In a normal subject artificially induced tachypnea resulted in a 17.5% basal metabolism increase. The author suggests that probably the increased work of the heart and of the muscles of respiration are the cause of the heightened basal metabolic rate in organic heart disease with decompensation. He also suggests the possibility of the thyroid factor as additionally causative, i. e., the transient hyperthyroidism during decompensation or changes in the thyroid circulation from long-standing congestion.—I. B.

**Striopallidal and bulbar symptoms in exophthalmic goiter.** Klein, H., *Monatschr. f. Psychiat. u. Neurol.* 65: 138. 1927; *Abst. Arch. Neurol. & Psychiat.* 19: 358. 1928.

Klein calls attention to the frequent association of exophthalmic goiter with organic diseases of the central nervous system, especially those involving the striopallidal and bulbar regions. He reports a case in which the symptoms referable to the central nervous system ran roughly parallel to the periods of remission and exacerbation of the exophthalmic goiter. Improvement of both symptom groups was marked after each of two operations (partial thyroidectomy). Eventually, certain of the symptoms of exophthalmic goiter disappeared (tachycardia) while others persisted (exophthalmos). The encephalopathic symptoms grew progressively worse. On the basis of this and other cases, as well as because of the relatively frequent finding of intracranial (especially bulbar) hemorrhages at autopsy, he believes that the central nervous lesions are the result of the toxin present in exophthalmic goiter.

The conditions under which iodine will cause a change in the basal metabolic rate in man: I. Its occurrence in conditions other than that of Graves' disease. Martin, K. A., *Am. J. M. Sc.* 174: 648-660. 1927.

The effects of large doses of iodine on the basal metabolic rate in patients with leukemia, polycythemia, primary anemia, rheumatic fever, simple goiter and hypothyroidism were studied. It was demonstrated that iodine will lower the basal metabolic rate in certain clinical conditions other than Graves' disease. The increased metabolic rate of patients with leukemia and polycythemia was not affected by ingestion of large doses of iodine. But, the high basal metabolic rate of patients with primary anemia and rheumatic fever was lowered, similar to the results seen in Graves' disease when iodine was given. Furthermore, moderate but constant lowering of the basal metabolic rate, from normal to a subnormal level, was observed when iodine was given to patients with simple goiter showing symptoms of iodine deficiency. Iodine will frequently increase the basal metabolic rate in patients with hypothyroidism or myxedema, providing they have not previously had iodine or thyroid therapy for several weeks. It is concluded, that since iodine is not a specific for Graves' disease in lowering the basal metabolic rate, the mechanism by which the basal metabolic rate is lowered, followed the ingestion of large doses of iodine, is an acute mechanical blocking of the thyroid secretion. The extent to which iodine will affect the basal metabolic rate in any patient, regardless of the diagnosis, depends upon the ability of the patient's thyroid to store iodine.

—Author's Abst.

The effect of hyperthyroidism on the development of intersexual forms in chickens (*Influence de l'hyperthyroïdisme sur l'origine des formes intersexuelles chez les Poules*). Nevalonnyj, M., *Compt. rend. Soc. de Biol.* 97: 1745-1749. 1927.

Dried thyroid was fed over a period of 147 days to 41 chickens varying in age at the start from 18 to 38 days. Four breeds of chickens were used. The plumage showed in each sex modifications to an intersexual type.—J. C. D.

Endemic goiter in Oregon. Olesen, R., *Public Health Reports*, 42: 2831. 1927; Abst., *J. A. M. A.* 90: 61.

The thyroid survey made by the author in Oregon included 8,171 boys and 9,427 girls attending the senior and junior high schools and the upper grades of the grammar schools in 32 localities. A total of 5,443 enlargements of the thyroid, a percentage of 30.9, was noted among the 17,608 children examined. Thyroid enlargements of all degrees prevailed among the boys to the extent of 22.3%, and among the girls to the extent of 38.3%. The observa-

tion previously made that thyroid enlargements decrease in numbers as boys increase in age, while among girls the involvements continue to increase in number up to the age of 18, was sustained by the survey. Endemic goiter is present to a considerable extent in the seacoast towns of Oregon, mere proximity to the ocean apparently failing to confer the relative freedom from the disease which prevails on Cape Cod, Massachusetts. At the same time there is much less goiter in the seacoast towns in Oregon than in the cities and towns farther inland. The places of birth and the places of previous residence are factors which do not appear to enter into the question of thyroid status among the children of a given community in Oregon. There appears to be no relationship between the amount of goiter in a given community in Oregon and the treatment of the public water supplies by filtration and chlorination. Endemic goiter prevails to a considerable extent in most portions of the state of Oregon. There is much less goiter in Oregon than in Minnesota, approximately the same amount as in Cincinnati, and much more than in Connecticut and Massachusetts. Olesen suggests the probability that iodine prophylaxis has materially altered the usual incidence of goiter in many localities. It may no longer be possible to determine natural goiter rates.

**The effect of iodine on creatinuria in hyperthyroidism.** Palmer, W. W., *Proc. Soc. Exper. Biol. & Med.* 25: 229-230. 1927.

In fifteen cases of true Grave's disease, with a daily creatine excretion of 200 to 1000 mgm., the administration of iodine in the form of Lugol's solution caused a diminution of creatine excretion to less than 100 mgm. In five cases of toxic adenoma relatively small amounts of creatine were observed in the urine, and iodine had almost no effect upon the excretion. The creatinuria of experimental hyperthyroidism was uninfluenced by iodine.—M. O. L.

**The thyroid gland in young adults (über die Bedeutung der Schilddrüsenvergrößerung im jugendlichen Alter für die Konstitution).** Rubens, O., *Ztschr. f. Konstit.* 13: 593-601. 1928.

Out of 3000 students, 19-22 years of age, at the University of Freiburg, 728 or 24.3% had enlarged thyroids, mostly of a soft diffuse variety, rarely nodular. Sixty to seventy-five per cent of those with slightly or moderately enlarged thyroid glands were from districts outside of Baden; while 60-70% of those with large and very large glands were from Baden. Body weight and stature of students with an enlarged thyroid were essentially the same as in students with a normal thyroid. The pulse rate while at rest was 6-7 beats per min. higher in students with enlarged thyroids. The pulse rate after exercise and respiratory rate in cases of enlarged thyroids were the same in cases with normal thyroids. Function-



ally it appears that enlarged thyroids are correlated with a slight degree of hyperthyroidism.—A. T. R.

**Acid base equilibrium in thyroid disease** (*El equilibrio acidobásico en las afecciones del tiroides*). Saida, M., *Arch. Endocrinol. y Nutrición*, 6: 279-283. 1926.

The acid base equilibrium has been very little studied in thyroid disease. The author has investigated this in ten cases and his findings coincide with those published by Walinski and Herzfeld. In nine cases of hypothyroidism of various types the alkaline reserve was studied by Van Slyke's technic. Low values were found. In one case of hypothyroidism a normal titre was found. There appeared to be no clear relation between the degree of acidosis and either the intensity of the clinical status or the level of basal metabolism. It is surmised that the decreased alkaline reserve is due to augmented formation of acid products and diminution of the blood pH in consequence of the augmented oxidation characteristic of hypothyroidism. He has had successful results in the treatment of hypothyroid condition accompanied by acidosis with insulin and large doses of alkali.—E. B.

**The effect of thyroxin in disorders related to the glands of internal secretion** (*Über die Wirksamkeit des Thyroxin (Schering) bei endokrin bedingten Störungen*). Schittenhelm, A., and B. Eisler, *Klin. Wchnschr.* 41: 935-938. 1927.

The authors made observations to ascertain the comparative effects of thyroxin and thyroid-gland preparations, administered intravenously and by mouth, on both healthy and pathologic human beings. In normal subjects thyroxin increased metabolism. Similar results were obtained in severe cases of myxedema, the patients being restored almost to normal. Intravenous use proved more effective than by mouth, but the latter is preferable in chronic cases. Thyroxin appeared preferable to thyroid-gland preparations since the latter cannot be so readily standardized and are likely to produce undesirable accompanying effects.—E. P. Durrant.

**The results of one hundred consecutive cases of hyperthyroidism operated upon.** A clinical and histological study attempting to correlate the morphology and clinical picture, with a view to prognosis. Smith, L. W., H. M. Clute, and J. W. Striedler, *Surg. Gynec. Obst.* 46: 325-331. 1928.

Relief from hyperthyroid symptoms was complete in 92 cases; the remainder were all much improved. After one year the basal metabolic rate of 19 patients was less than —10% and of these 15 showed clinical symptoms of myxoedema. This result is considered to be due to removal of larger amounts of gland than was done

formerly, and to administration of iodine after operation to prevent hyperplasia. There is little apparent relation between the degree of involution of the gland and the basal metabolic rate or the clinical picture. The pre-operative administration of iodine is one of the chief factors in disturbing this relationship. There is no relationship between the degree of involution and incidence of either lymphoid infiltration or acidophilic cell formation. Acidophilic cells in hyperplastic glands have been found in all the cases which subsequently developed myxoedema.—A. T. C.

**The treatment of habitual abortions by thyroid extract (*Le traitement de l'avortement habituel par l'extrait thyroïdien*).** Vignes, H., *Progrès méd.* 42: 1255. 1927.

One case report includes the details of three miscarriages occurring at two and one-half, three, and eight months. A weakly positive Hecht reaction led to rather extensive anti-luetic treatment with no improvement in the tendency to abort. Following the third miscarriage, there was sterility for two years. One month after beginning treatment with thyroid extract, pregnancy occurred. A normal full term child was born. The author concludes that slight hypothyroidism is sufficient cause to produce abortion. Also, when slight hypothyroidism is the cause of abortion, the administration of thyroid extract will correct the condition sufficiently to permit normal pregnancy.—J. P. Pratt.

**Effect of iodine in toxic adenoma.** Youmans, J. B., and R. H. Kampmeier, *Arch. Int. Med.* 41: 66-74. 1928.

The response to treatment with iodine in thirty unselected patients with toxic adenoma who were previously untreated with iodine was essentially the same as that seen in unselected cases of exophthalmic goiter. Whatever differences exist are apparently quantitative, not qualitative. No essential difference in the pathogenesis of toxic adenoma and exophthalmic goiter can be assumed to exist on the basis of this response to treatment with iodine.—Authors' Abst.

# Endocrinology

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STUDIES OF THE ENDOCRINE GLANDS  
III. THE THYROID

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## PART I

In a recent publication (1) the authors have discussed the results obtained from the study of a group of pituitary cases by the application of a general method of diagnosis, the details of which have recently appeared (2). This present communication deals with the findings in a series of cases presenting some phase of thyroid disease as the principal etiological element. As the establishment of criteria of performance and methods of approach have been discussed in detail in the earlier papers, attention may be directed at once to the present thesis.

## INTRODUCTION

With the sole exception of the pancreas and its endocrine malfunction producing diabetes, no one of the proven ductless glands has been so thoroughly and successfully studied as has

the thyroid.\* The early recognition of the association of the two classic syndromes, exophthalmic goiter and myxedema, with aberrant function of the gland, is a most important factor. Even more important has been the development of an unimpeachable surgical technique for the control of hyperfunction, and equally, the demonstration of the efficacy of preparations of the gland to correct lowered activity by a replacement therapy. The preparation by Kendall (3) of a single substance capable of duplicating in large measure the pharmacologic action of the glandular extract, is the latest step in the development. In advanced Graves' disease, long-standing myxedema, or well-established cretinism, the several pictures presented conform so nearly to the classic type that diagnosis is relatively simple and certain. In incipient or even intermediate stages, however, many cases present which may not be accurately traced to a thyroid malfunction. Further, in a not inappreciable number of individuals, thyroid disease may present a chain of symptoms utterly at variance with the classic types, and these will certainly escape proper diagnosis if only subjective findings are considered. Two pitfalls, grave at least for the patient, must sedulously be avoided. In many metabolic disturbances, end results in the form of symptoms may be suggestive of thyroid malfunction. To confirm these indications by a single test—the basal metabolic rate—and by its sole authority to establish a diagnosis, is an entirely unwarrantable procedure. Several non-endocrine conditions simulate one or another form of thyroid disease and may even exhibit a seemingly characteristic change in the metabolic rate. Differential diagnoses can be established only after complete and diversified study of the case, interpreting subjective evidences in the light of objective facts.

The endocrine glands are among the important regulators of metabolism. It is not remarkable then that disturbance of two wholly unrelated foci of control may produce a common end result. The cheery optimism of the speculative endocrinologist who sees a definite endocrine element in some obscure condition because of a single symptom also associated with some classic endocrine syndrome, does not make for progress. That

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\*This statement does not imply a failure to recognize the vast amount of animal experimentation involving the suprarenal bodies. So much of this work, however, is inapplicable to human problems involving these glands that, in this restricted sense, the above statement is felt to be warranted.

many hypothyroid subjects exhibit obesity, does not connote a thyrogenic origin of all obesity. Due tribute must be paid to what may be euphemistically designated as a hearty appetite, to say nothing of the several pathological obesities in which the thyroid has no part. The promiscuous and injudicious use of thyroid extract to combat this conditions has, like King David, slain its tens of thousands. The presence or absence of thyroid enlargement is absolutely no criterion. Severely toxic and practically inert thyroids of normal size are observed daily, while the massive hyperplasias of the endemic goiter frequently are associated with a completely normal bodily function. The tale could be lengthened indefinitely, but enough has been said to indicate that the diagnosis of atypical, incipient, and obscure thyroid conditions requires a most careful and complete differential survey. The exclusion of non-endocrine disorders is no less important than the inclusion of an hormonal aberration, and should precede it.

As is patent from the character of the data, and as has already been stressed (2), the presentation, in collected form, of data inherently self-contradictory, offers difficulty. Averages can be employed only when the composing units have the same sense and differ only in magnitude. An average composed from a judicious selection of + and — observations, could only present a wholly misleading normality. On the other hand, case series must be of sufficient length to merge individual differences of extraneous origin and indicate the true trend of the observation. For purpose of clarity in presentation and waiving the nice points of an ever active controversy, in the following discussion we shall designate as “hyperfunctional” (+) all cases presenting a uniform picture of what is generally regarded as an over-activity. Conversely, “hypofunctional” (—) cases present the antitheses of the foregoing. The intermediate group, in which are merged individual symptoms portrayed by the two extreme conditions, we shall designate as “dysfunctional” ( $\pm$ ). In this later group are to be found those cases in which an initial hyperactivity is undergoing a functional involution (transition states) with an unequal rate of recession of the several salient characteristic features. In taking this position, we hope to avoid argument that can only obscure the principal aim of the thesis. Incidentally, this attitude is a not uncommon one among the serious workers in this field.

## OBSERVATIONS

Following a practice established in the earlier papers, first consideration will be given to the physical measurements of the several groups. The data are collected in Table I.

TABLE I  
Physical Measurements

Observation	Unit	Gland Function			Grand Average
		—	±	+	
Number of Cases.....		126	53	21	200
Sex—Male .....	%	29	17	33	27
Female .....	%	71	83	67	73
Age—High .....	Years	74	66	70	
Low .....	Years	8	8	18	
Average .....	Years	37	33	44	37
Height—High .....	cm.	189.5	181	176	
Low .....	cm.	134	131.5	148.5	
Average .....	cm.	164	159	165	163
Sitting Height—High .....	cm.	97	93	93.5	
Low .....	cm.	71.5	73.5	80.5	
Average ...	cm.	87	85	87	86
Sitting Height Index.....		0.530	0.535	0.527	0.531
Chest—High .....	cm.	150	99	93.5	
Low .....	cm.	57	64.5	62.5	
Average .....	cm.	83	77	78	81
Weight—High .....	kgm.	156.6	100.0	73.8	
Low .....	kgm.	30.6	31.3	40.8	
Average .....	kgm.	65.1	59.5	58.7	62.9
Area—Average .....	sq.m.	1.71	1.61	1.65	1.68
Lung Volume—High .....	cc.	5380	3720	4600	
Low .....	cc.	1100	1350	820	
Average ...	cc.	2840	2570	2310	

The allocation of cases to the several groups offers a statistic that is potentially misleading. The cases here presented were seen in the course of a consulting diagnostic service. Hyperactivities of the gland are usually too well defined to require elaborate analysis for diagnosis. Our studies on this group lack certain of the tests comprehended in the usual case analysis, and for this reason have been omitted from the tables including them. The relative proportion of dys- and hypo-functional cases to each other is probably more representative.

The dominant incidence of thyroid disease in the female has been noted by many (4, 5), the Mayo Clinic reporting 85 per

cent females in nearly three thousand cases, while Sattler's compilation shows an equal (82 per cent) incidence. The same general trend is manifest in the hypo-functional group, though sex disparity is much less in the hypothyroidism of childhood. The age averages possibly show the tendency for the hypofunctional condition to occur earlier in life, but the lower average age of the dysfunctional group (containing many transition cases) is inharmonious. With thousands instead of hundreds of cases these discrepancies would probably disappear. The practical elimination of young cretins from this series certainly raises the average age of our hypofunctional group. This same factor undoubtedly operates in fixing certain of the other measurements, notably the standing height, at the relatively normal levels observed. In fact, our data are to be regarded as giving a picture of the incidence of thyroid disease in adult life when certain of the growth inhibitions are no longer operative. The weights here recorded, on an average, do not indicate the dominance of obesity usually associated with decreased function. The inclusion of a number of the thin amyxedemic thyroid failures—a syndrome identified by us and to be described later in this paper—unquestionably influences the average and renders it less representative of the classic type. The extremes observed for the several measurements are significant, and it is perhaps pertinent, in the light of the foregoing, to call attention to the fact that both the highest and lowest absolute values are found in the hypofunctional group. In some instances, relative exceed absolute values in significance, and in the next table are given the weight-chest-lung volume comparisons made under conditions outlined in the first paper.

Over one-third of our outspoken thyroid failures are underweight, although in deriving a net average for the group they are completely absorbed. These several net averages show a tendency from group to group, as do the relative percentages of the moieties of each above and below the predicted values. The chest measurements give no evidence of the characteristic distribution of weight, although, as has been shown earlier, the female chest-hip ratio exhibits significant differences.

The average thyroid subject shows a loss of lung volume from the predicted level which is truly significant. Bryson's (6) observation that chest expansion is limited, may bear upon

this finding. That it is not solely due to fatty infiltration, as claimed by Askanazy (7), is demonstrable by comparison with the obese of other than thyroid origin. The full magnitude of the deviation in many cases is somewhat obscured in our averages by the inclusion of a significant number of incipient cases. A marked loss (40 to 60 per cent) of predicted lung volume is a common finding in cases offering no other cause for the phenomenon than the thyroid disease.

TABLE II  
"Vital Capacity"

Observation	Unit	Gland Function			Grand Average
		—	±	+	
Weight—High .....	%	+247	+78	+27	
Low .....	%	—38	—29	—25	
+ Average .....	%	+23	+19	+13	
% .....	%	64	56	43	
— Average .....	%	—14	—11	—14	
% .....	%	36	44	57	
Net Average.....	%	+10	+6	—3	+7
Chest—High .....	%	+96	+26	+17	
Low .....	%	—21	—15	—23	
+ Average .....	%	+12	+11	+7	
% .....	%	64	47	62	
— Average .....	%	—7	—6	—12	
% .....	%	36	53	38	
Net Average.....	%	+5	+2	±0	+4
Lung Volume—High .....	%	+19	+25	+6	
Low .....	%	—70	—47	—75	
+ Average ....	%	+6	+13	+6	
% .....	%	11	8	5	
— Average ....	%	—25	—25	—41	
% .....	%	89	92	95	
Net Average...	%	—22	—22	—39	—24

Such urine findings as may be offered in tabular form are grouped in Table III.

The urine volume has a somewhat downward tendency, and the total elimination in the hypofunctional group tends to be inadequate. Coupled with this is a high incidence of small amounts of albumin and, as will be seen later, a blood picture suggesting retention. To these general indices we have applied the term "pseudonephritis," as other signs of kidney impairment are wanting and both the blood and urine picture attain



to a continued normality under treatment. Falta (8) comments on the small volume and slight albuminuria, and ascribes them to nutritive disturbances of the kidneys. Another possible explanation might be a deposition of the mucin-like substances that have been identified in other parts of the body and in the kidney by Halliburton (9) and others. Broadly speaking, lowered elimination, slight albuminuria, and not infrequently the appearance of casts, is generally recognized as of relatively high incidence in the several forms of thyroid disease. Our own figures would seem to indicate a tendency toward their appearance with failing thyroid function.

TABLE III  
Urine Measurements

Observation	Unit	—	Gland Function ±	+	Grand Average
Volume—High .....	cc.	4350	3090	2060	
Low .....	cc.	340	360	470	
Average .....	cc.	1090	1050	1090	1080
Spec. Grav.—High .....		1.036	1.036	1.028	
Low .....		1.002	1.007	1.007	
Average .....		1.019	1.021	1.019	1.020
Albumin .....	%	29	25	11	26
Casts .....	%	16	21	11	17
Sugar .....	%	7	17	16	11
"Urobilinogen"* .....	%	5	3	0	4
Amylase Index—Av.....		17	15	—	
Salol—Av. ....	min.	103	70	—	91
Urea Curve—Normal .....	%	67	70	—	67
Delayed .....	%	4	20	—	8
Progressive ..	%	4	0	—	3
Low .....	%	25	10	—	22
Phenol-Sulphone-Phthalein, 2 hour Elimination—Av..	%	53	57	59	

\*Positive tests due to concomitant liver involvement. See text.

The question of glycosuria is a moot point and one that even today is far from a state of general agreement. As early as 1907 v. Noorden (10) commented on an occasional appearance of sugar in the urine of myxedemias—this, too, in a condition generally recognized as raising the sugar tolerance. Falta (8) cites a personal observation at some length of a myxedemic who showed slight alimentary glycosuria even after treatment had been suspended for two months. He infers simultaneous pancreatic involvement, also a possible complicity of the hypophysis, and offers this explanation to account for the same carbohydrate anomaly

as reported by several other observers. Blood sugar values are lacking. Several other explanations offer themselves as being, at least, equally plausible. First, if it be conceded that the thyroid exercises any control over carbohydrate metabolism—and this is scarcely a debatable point—it must be remembered that many cases are seen of patients in a transition state between an earlier hyper- and a final hypo-activity. As all of the functional disturbances characteristic of the first state do not recede with the same velocity, a picture inevitably results which lacks the definition of either of the initial or terminal phases and

TABLE III-a

No.	Sex	Basal Met. Dev.	Gal. Tol. Dev.	Blood Sugar	Remarks
B-169	F	—20	±0	102	
234	M	—11	±0	92	Earlier thyrotoxicosis (Goiter).
267	F	—10	+25%	94	Earlier thyrotoxicosis (Goiter).
528	M	—29	±0	100	Psychosis (manic depressive).
559	F	—26	±0	83	Obesity.
S-531	F	—13	—	83	Pregnant. Had been under intermittent Thyroid medication for years.
640	F	—21	Incomplete Not < N	104	Otosclerosis.
685	F	—16	±0	133	Blood sugar level due to emotion. Patient nervously very unstable, which fact probably influenced the observed basal rate to some extent.
1013	F	—26	Incomplete Not < N	100	Sterile. Became pregnant after thyroid medication.

includes features of both. A full discussion of this question is shortly to appear elsewhere, and in the interest of brevity will here receive no further mention. A second possibility in Falta's case, as well as others simulating it, lies in his report of an earlier jaundice. Scattered through the literature are occasional references to liver disorders complicating thyroid disease. We shall discuss such a group in a subsequent portion of this paper. It is well known that certain types of liver involvement lower the sugar tolerance to a very appreciable degree. Frankly, in Falta's case the liver would have to be excluded before credence could be given to the complicity of a multiglandular concert.

In the present instance, because of the diversity of opinion on this point, a further analysis of the anomalous cases may be permitted. This can be confined to the pure hypofunctional group, as the anomaly really exists only with its composing members. The significant facts can be offered most compactly in tabular form.

Of the nine cases presenting, three subjects, namely, B-234, B-267, and S-531, can at once be eliminated as the first two have histories of earlier hyper-activity, and the third is pregnant. The first two are included in the hypofunctional group as the glycosuria represents the only departure exhibited, and the residual picture was clear-cut thyroid failure. The other six cases all show normal blood sugar levels and a galactose tolerance that in no case is below normal. True, the metabolism of galactose varies in some measure from that of glucose, and the urine sugar is presumably the latter. In any case, there is nothing here to support either a pancreatic or hypophyseal complication. In all of the "B" cases the liver is ruled out by other observations, and in the "S" cases, by the implication of the normal sugar tolerance. As before stated, this question will be discussed elsewhere under more elastic space conditions.

TABLE IV  
Nitrogen Partition

Observation	Unit	—	Gland Function ±	+	Grand Average
Total Nitrogen	Av. gms.	8.32	8.59	8.79	8.44
Urea Nitrogen	Av. %	78.6	80.5	78.0	79.1
Uric Acid Nitrogen	Av. %	2.6	2.1	2.2	2.4
Ammonia Nitrogen	Av. %	4.0	3.8	3.9	3.9
Creatinin Nitrogen	Av. %	4.3	4.4	3.6	4.3
Residual Nitrogen	Av. %	10.5	9.2	12.3	10.3
%=or < 9%	%	64	54	67	61

"Urobilinogen," the probably non-specific response to the paradimethylamino benzaldehyde reagent of Ehrlich (11) was demonstrated only in cases exhibiting a concomitant liver disturbance. This will be discussed later. The urea curves synchronize well with the earlier evidences of loss of renal integrity which, however, the phthalein test fails to support. That this latter test is subject to many sources of error is recognized. Further, in the lowered permeability in many of these cases

there is not the loss of renal function that certain of the tests would imply. The delayed elimination of salol falls in this category rather than in that of a lowered gastric motility.

A complementary observation of urine composition comes in the determination of the formula of nitrogen distribution.

The average nitrogen elimination is low, both in comparison with other endocrine and with non-endocrine disorders. As these data represent typical 24-hour collections on the patient's usual diet, and not nitrogen metabolism experiments, they cannot be equated directly with the careful studies of Janney and Isaacson (12). They would certainly seem to confirm the latter's contention in regard to the rate of protein destruction in thyroid disease. If relative weights are considered, these data offer no support of Forschbach's (13) contention that the creatinin elimination is decreased in hyper-active states. The accuracy of this has previously been denied by others.

The relation of the other measured quantities accords well with accepted normal standards. Only the residual portion departs from convention, and that registers a level definitely superior to the established norm. Moreover, this increase is shown by three-fifths of the entire group of cases. That it is not due solely to the presence of creatin, as noted by McCrudden (14) and others, has been observed by one of us (15). Rather, there exists nitrogenous material of unknown composition which is demonstrable not only in the endocrinopathies, but in other pathologic conditions as well. Of the entire group of endocrine disorders, the thyroid shows the generally highest level of this quantity, both in average amount and frequency of incidence of fractions exceeding the conventional normal. It constitutes an important datum in the general compilation of facts leading to diagnosis.

Earlier in the paper we have spoken of the pseudonephritis frequently observed in cases of thyroid failure. The urine findings have already been discussed; the blood chemistry next claims attention.

Inspection of the average values given above would not seem to confirm the statement that the blood gives evidence of retention. Two points, however, must be borne in mind. First, the level of protein metabolism in these cases is low as gauged by the total nitrogen of the urine. In the light of careful metabolism

studies, among others of Boothby and Sandiford (16), and Janney and Isaacson (12), this would seem to be due to diminished intake and absorption rather than to any characteristic change in the catabolic phase. It is demonstrable that low protein metabolism lowers levels of blood nitrogen, just as high utilization determines increase. The blood picture, however, varies

TABLE V  
Blood Chemistry (and Serology)

Observation	Unit	Gland Function			Grand Average
		—	±	+	
Non Protein Nitrogen	Av. mgm.	31	33	29	31
% > 35 mgm.	%	28	30	6	25
Urea Nitrogen	Av. mgm.	16	15	15	16
% > 17 mgm.	%	23	18	20	22
Uric Acid	Av. mgm.	3.6	3.4	3.6	3.5
Net <sup>1</sup> % = or > 4 mgm.	%	20	14	22	19
Creatinin	Av. mgm.	1.4	1.5	1.5	1.4
Residual Nitrogen	Av. mgm.	13.2	16.3	12.2	15.3
Sugar	Av. mgm.	96	102	97	97
% > 120 mgm.	%	1	6	5	3
% < 80 mgm.	%	6	0	11	5
+ Wassermann	%	0	0	5	0.5
+ Kahn (presumptive)	number	0	0	0	
+ Spinal Fluid	number	1 <sup>2</sup>	0	0	1
+ Schwartz-McNeil	number	0	0	0	

<sup>1</sup> All demonstrated cases of nephritis and gout have been deleted.

<sup>2</sup> Non-luetic.

within much narrower limits than may be conditioned by the protein exchange.\* Second, individual cases showing relatively high values lose their identity when merged by averaging with a number of observations which do not exhibit the condition. The significance of relative values should be stressed. A non-protein nitrogen of 35 mgm., absolutely normal by accepted convention, is relatively high for an individual excreting less than 6 grams of nitrogen in twenty-four hours. Further, one-fourth of the cases of this series showed values for non-protein nitrogen in excess of 35 mgm., paralleled by an almost equal incidence of urea nitrogen values in excess of the conventional norm. Fifty cases showed uric acid equal to or above 4 mgm., but of these, eighteen gave other evidences of true nephritis and are deleted in the tabular presentation. The contention, then, has a measure

\*One of us (Rowe and Walker, unpublished data,) has produced changes of blood nitrogen of the order of 15-20 per cent in normal subjects by adding from 100 to 200 per cent of additional protein to a maintenance ration.

of reason when due allowance is made for the limitation of this form of presentation.

A point of interest, for which we can offer no explanation at present, is the somewhat low value of the residual nitrogen in the terminal groups. The somewhat high value of the dysfunctional cases brings the total average to a normal value.\* Of the several blood constituents, the sugar is the only one which has received any extended record in the literature.

This is presumably due to the influence of the thyroid on carbohydrate metabolism and the general use of the sugar curve method to determine tolerance. Sharp differences of opinion as to the fasting level of blood sugar and the complication introduced by comparison of fasting levels with those resulting from sugar alimentation, has stimulated study, albeit, in some instances, of a somewhat uncritical character. Without detailed analysis of the somewhat diffuse literature, it may be said that a careful survey would seem to indicate no hyperglycaemic effect of thyrotoxicosis in man, and, equally, a slight hypoglycaemic tendency in thyroid failure. The figures given above show that the averages of all three groups conform straitly to the conventional normal. This is even more strikingly illustrated by a selection of extreme cases drawn from the above group and collected in Table V-a.

TABLE V-a  
Blood Sugar Levels

Observation		Hypo- function	Hyper- function
Number of Cases		—	+
Basal Metabolism Deviation—High	%	—30	+87
Low	%	—50	+44
Average	%	—36	+65
Blood Sugar (fasting)—High	mgm.	115	108
Low	mgm.	71	78
Average	mgm.	91	92
Number below 80 mgm.		5	1

Inspection of the figures given above fails to demonstrate any specific thyroid influence on blood sugar levels. True, these selected averages are lower than those of the entire groups, but

\*Calculation of a large number of analyses of normal bloods would fix 15 mgm. as a fair average with a  $\pm$  variation of perhaps 2 mgm. On this basis all of the values fall within the normal range.

it must be remembered that these cases represent the maximum of nutritional disturbance and hence a lower nutritional level. Not impossibly, a failure to take due cognizance of the importance of the level of nutrition prior to a sugar test is responsible for some of the conflicting data elsewhere reported. Faulty technique is another definite factor. The cases here recorded were, in the main, on a liberal, standardized diet for a period of at least four days before the blood sugar levels were determined. Further, only morning fasting bloods were taken, the foodless interval approximating fifteen hours.

Reverting to Table V, it will be noted that one of the hyperthyroid subjects gave a positive Wassermann reaction. The case was one of well-marked, typical exophthalmic goiter, with all of the classic signs. The luetic element here is concomitant only as affecting the general picture. In a second patient, the positive spinal fluid gave a gold curve of the meningeal type. No luetic element could be demonstrated or elicited.

In contradiction to the blood chemistry, numerous observations exist on the influence of thyroid disease on the blood morphology. The earlier reports tend to stress an anaemia in Graves' disease, leucopenia and an increase in the lymphocytes and monocytes at the expense of the neutrophilic elements. Likewise, descriptions of the myxedemic picture reiterated the anaemia, leucopenia and lymphocytosis. Later observers have failed to confirm these findings in their entirety, and in several points there still exists a marked difference of opinion. In the first instance, Plummer (17) in a long series has failed to confirm the monocyte increase and the leucopenia. There is a slight anaemia, tendential rather than established, and a moderate relative leucocytosis. Our own data are assembled in Table VI.

In all of the groups the values for haemoglobin and erythrocytes are normal, although tending downward. Lymphocytosis is found throughout, although the distribution is opposite to that observed by Falta, who found it more pronounced in the hyper-active cases (8).

Likewise, the eosinophilia recorded by him is not manifest, nor do the monocytes exceed the limits of normality. While it is generally recognized that the blood picture does not correlate with the severity of the condition, an analysis of the same group

of extreme cases, collected in Table V-a, may not be devoid of interest.

These values equate well with those of the preceding Table (VI), although slight differences are apprehensible. The anaemic

TABLE VI  
Blood Morphology

Observation	Unit	Gland Function			Grand Average
		—	±	+	
Haemoglobin	Av. %	87	87	88	87
Erythrocytes	Av. 10 <sup>6</sup>	4.84	4.87	4.94	4.87
Color Index		0.90	0.89	0.89	0.90
Leucocytes	Av. 10 <sup>3</sup>	7.5	8.2	7.2	7.7
P. M. N. Neutrophiles	Av. %	56	57	60	57
%=or > 75%	%	2	12	5	
Lymphocytes	Av. %	38	35	33	37
%=or > 33%	%	66	54	43	60
Eosinophiles	Av. %	2	2	2	2
Net %=or > 3% <sup>1</sup>	%	19	27	11	20
Monocytes	Av. %	4	6	5	4

<sup>1</sup> Cases in which a non-endocrine cause of eosinophilia was demonstrated have been deleted.

tendency is slightly more marked, the leucocytes are slightly lower, and the monocytes and lymphocytes higher in the hyperactive group. Barring the monocytes, our figures agree well with those of Plummer, which carry conviction, as they are based upon nearly one hundred times as many cases. With the hypoactive cases, the leucocyte value is even more normal, the lymphocytes go to a slightly higher level, the monocytes remain unchanged. A slight increase in eosinophiles brings this point

TABLE VI-a

		Hypofunction	Hyperfunction
Haemoglobin	%	87	84
Erythrocytes	10 <sup>6</sup>	4.71	4.59
Leucocytes	10 <sup>3</sup>	8.0	6.7
Neutrophiles	%	52	55
Lymphocytes	%	41	37
Eosinophiles	%	3	1
Monocytes	%	4	7

more nearly in accord with Falta's observations, but falls far short of the really significant magnitudes recorded by him.

Seemingly, the lymphocytosis is the only point of real departure from the generally accepted normal adult picture, and



this is found in practically all of the endocrine states and in not a few non-endocrine disorders. The magnitude of the relative increase is somewhat greater in thyroid than in the other named conditions.

The respiratory metabolism and its usual expression in the basal metabolic rate, constitutes a chapter of the greatest importance in the diagnosis of thyroid malfunctions. Taken as a sole criterion, usually it is wholly inadequate to establish a diagnosis; considered as one observation in a group, it probably has more individual significance than any other single test, with the possible exception of the sugar tolerance. And this statement presupposes a careful and complete clinical analysis of the case as intrinsic in any diagnostic procedure.

From the initial observations of Magnus Levy (18) that thyroid disorders were associated with marked changes in the oxygen consumption, an extensive literature has come into being. In the interest of brevity, no attempt will be made to review the earlier work; the discussion will be confined to our own observations, since they constitute a part of the general diagnostic scheme. The data are found in Table VII.

Following the convention earlier defined, we find the uncomplicated hypoactive states showing an oxygen consumption rate equal or inferior to 10 per cent below the predicted value. Similarly, the established hyperfunctional cases range from  $+19$  to  $+87$  per cent. The points of emphasis lie in the direction of the change, and more importantly in the amount. While other disorders may condition significant changes, but few approach in magnitude those of thyroid origin. And with these—diabetes with great emaciation and Addison's disease on the one hand, and the leukaemias and high fever on the other—a few relatively simple additional observations will permit of a ready differentiation. As has been discussed elsewhere (2) of the endocrine concert, only the adrenal approaches the level of myxedema in its failure, and even here it falls appreciably short of the low levels which severe thyroid inactivity can engender. While the lowest level recorded in this series is  $-50$  per cent, we have recorded cases falling nearly 10 per cent lower. A few similar observations have been recorded by others.

The blood pressure values show a definite gradation in the sense of the basal rate. The picture in the hypothyroid group.

is complicated by the fact that in the later stages arteriosclerosis tends to raise blood pressure from the initial low to a final hypertensive level. In any average such as the present, which includes all chronological phases, a few arteriosclerotics will raise the average appreciably. This is well illustrated in the sequence of the percentages of low values for the systolic pressure. As is to be expected, the diastolic readings are less influenced. The

TABLE VII  
Respiratory Metabolism

Observation	Unit	—	Gland Function ±	+	Grand Average
Basal Metabolism					
Deviation					
High	%	—10	+18	+87	
Low	%	—50	—31	+19	
+ Average	%	—	+11	+42	
%	%	0	19	100	
— Average	%	—24	—14	—	
%	%	100	81	0	
Net Average	%	—24	— 9	+42	
% > +10 %	%	0	6	100	
% between +10% & —9%	%	0	39	0	
% = or < —10 %	%	100	55	0	
Blood Pressure:					
Systolic Av.	mm.	114	120	138	
% < 110 mm.	%	54	32	10	
Diastolic Av.	mm.	71	74	70	
% < 65 mm.	%	33	26	50	
Pulse Rate: Av.	Per min.	66	79	101	
% = or < 80 per min.	%	8	45	81	
% = or > 70 per min.	%	70	21	0	
Respiration Rate: Av.	Per min.	15	16	18	
% = or < 10 per min.	%	9	4	10	
Temperature: Av.	Deg. F.	97.7	98.2	98.2	98.0
Alveolar CO <sub>2</sub> : Av.	mm.	39	38	37	38
% > 35 mm.	%	78	65	67	74
% = or < 30 mm.	%	5	8	14	7

pulse rate sequence is also striking and of the order to be expected. Very slow heart rates are usually associated with established failures, although with mounting blood pressure there is a tendency for the pulse to augment. These trends do not synchronize, however, and constitute one of the several elements leading to the contradictory picture of the transition state. The rapid breathing, frequently concomitant with the tachycardia of Graves' disease, finds tendential expression in the values given above. Likewise, the hypothermia of the established failure is

indicated. It must always be borne in mind, as earlier noted, that in any compilation such as the present, the extreme findings of the terminal state are minimized materially by the inclusion of the incipient and developing cases. Trends, therefore, take on an added significance.

The prevailing tendency of the alveolar CO<sub>2</sub> tensions is toward the normal. The sub-normal tensions observed are possibly influenced by the measure of the patient's co-operation,\* and in the over-active cases rapid breathing may condition some CO<sub>2</sub> deficit. The Fredericia method was used throughout, earlier

TABLE VIII  
Galactose Tolerance

Observation	Unit	Gland Function		Average
		—	±	
Male				
Dose:	High Gms.	40	30	
	Low Gms.	30	20	
	% above normal	13	0	
Average deviation of dose	%	+33	—	+33
	% equal normal	87	33	
	% below normal	0	67	
Average deviation of dose	%	—	—33	—33
Female				
Dose:	High Gms.	60	40	
	Low Gms.	40	20	
	% above normal	33	0	
Average deviation of dose	%	+31	—	+31
	% equal normal	67	63	
	% below normal	0	37	
Average deviation of dose	%	—	—29	—29
Summary				
	% above normal	25	0	18
	% equal normal	75	56	69
	% below normal	0	44	13
Average + Deviation (1)	%	+32	—	
Average — Deviation (1)	%	—	—31	

(1) Not weighted for relative number of cases.

study (19) having demonstrated its relative dependability. Failure to expel the air thoroughly will give a sample diluted by the tidal phase.

The last laboratory observation to be considered, the sugar tolerance, equates with the basal rate in diagnostic importance—and is equally unfitted to be a sole and final arbiter.

For reasons which have already been discussed, galactose was selected as the vehicle for the tolerance test. That it un-

\*In a few cases it was possible to demonstrate this element.

doubtedly has a different metabolic cycle from glucose may be freely admitted. The chief aim was, however, to devise a sugar tolerance test which should be simple, easily applied, and, most importantly, clear cut in its indications. That galactose complies with these criteria has been amply demonstrated, while the intrinsic differential sex influence is an added advantage of great value. The majority of observations of sugar tolerance are based on glucose studies, and the greater part of these on the blood sugar curve method. As one of us (20) has shown, the so-called diagnostic curves of hyper- and hypo-thyroidism are readily reproducible in a group of established thyroid failures, or equally with normal subjects, by the use of dosages above or below the utilization capacity of the given individual. For example, Olmstead and Gay's (21) two differential curves were reproduced by us in a single group of myxedemics by the use of sub- and super-tolerance doses. The shape of the blood sugar curve is determined by the relation of the dose given to the individual tolerance, and at the best is but qualitative in its indications. The lack of dependence of the reaction to the test meal upon body weight has been stressed. For example, if the Janney and Isaacson technique (22) were followed in case of myxedemics whom we have studied and who were identical in all respects except body weight, one would have received 84, the other 218 grams of glucose. As it was, one responded to 40, the other to 50 grams of galactose. The curves elicited by test meals based on weight could not fail to be misleading in any quantitative sense.

The inclusion of quantities of other foods and of the juice of grapes or the citrus fruits is so patently undesirable as to require no discussion.

Review of the literature shows a variety of contradictions, but in the main it may be said that in existing hyperthyroidism the sugar tolerance is diminished, while the reverse obtains with the opposite terminal condition. Definite quantitative expression is usually lacking. Hirschl's (23) report of the failure of 500 grams of glucose to excite glycosuria in a group of myxedemics, equates with some of Miura's (24) observations. The interest here is in the physiological phenomenon of the retention of these massive doses rather than in a quantitative significance of the test.

Of tests with galactose, but few are recorded. Bauer (25), using 40 grams and requiring for his standard an elimination in excess of 3 grams, found two positive in nine cases of hyperthyroidism. Wagner (26), with the same dosage but positive response indicated by one gram, reported thirteen out of fourteen as positive. Strauss (27), with 30 grams, and Hirose (28), with 25, both using a qualitative urine test as the criterion of response, found, respectively, three in four and nine in nine to be positive in thyrotoxicosis. Neubauer (29) tested a group of cases after thyroidectomy, using 40 grams and an elimination greater than 0.9 grams as the criterion. Thirty-eight out of forty-five were positive, and only two failed to show some sugar.

Our own findings agree in sense with the foregoing, but differ widely in the quantitative expression. For reasons given in the table, no established cases of hyperthyroidism appear. A few isolated records, made in connection with other studies, would seem to indicate that the established hyperthyroid case exhibits either a normal or slightly depressed tolerance for galactose, of the same order of magnitude as observed in the dysfunctional group. This statement is tentative and is open to revision should an extended series of observations indicate necessity. Present information warrants the conclusion given above. Perhaps the most striking feature of the results is the dominantly large percentage showing a normal tolerance. Further, where deviation does occur, it is of a very moderate order in the uncomplicated cases. A few of our observations have been omitted from the general tabulation, as their inclusion could only serve to mask the general trend, and in each instance the anomaly was directly traceable to a non-endocrine cause influencing carbohydrate metabolism. The cases severally were those of one male giving positive response with 20 grams (a —33 per cent of deviation), and four women averaging a deviation of —68 per cent. They were all demonstrated thyroid failures and all equally had a demonstrated liver disorder to which the lowered tolerance was directly referable. In this connection it may not be inapposite to recall the fact that the first use of galactose for function testing was by Bauer (30) in 1906, and was offered as a means of evaluating liver involvement.

To summarize then, the status of galactose tolerance in thyroid disorders: Over two-thirds of the subjects show a normal

tolerance. When extraneous effects influencing tolerance can be excluded, the dose producing melituria, if altered, moves in opposite direction to the basal rate change and is always of moderate amount. These results agree qualitatively with other observations, but differ materially in the quantitative expression. The differential significance of this fact is patent.

There is yet another point in connection with the carbohydrate metabolism that may well be touched upon at this time. Earlier in the text, note was made of the occasional appearance of glycosuria in patients with demonstrated thyroid failure, seemingly uncomplicated by other factors which might influence the sugar assimilation limit. From the foregoing discussion, it is evident that the thyroid influence on carbohydrate metabolism in general is definite, but of a lesser order of magnitude than that of the pancreas, the pituitary or the adrenal. In a few cases, however, of unmistakable exophthalmic goiter, we have observed a profound influence on the assimilation limit usually associated with relatively small changes in the respiratory metabolism. The protocol of a typical case will be given and discussed in a subsequent portion of this paper. A possible explanation of the apparent anomaly could lie in the existence of a second thyroid hormone exercising an influence on sugar metabolism as does thyroxin, or its analogue, on the consumption of oxygen. This suggestion is offered tentatively; it will be discussed later in the paper.

## PART II. CLINICAL SECTION

### INTRODUCTION

The clinical section of this paper is based upon the analysis of a series of 100 consecutive cases which comprise part of the larger series reported in the previous section. The reasons for selecting the smaller group for clinical analysis are: First, that all the patients in it have been under the personal observation of one of us for sufficient time to demonstrate the effect of treatment, confirming the diagnosis; and, second, that the series can be fairly compared with an equal number of cases of pituitary failure already reported. All the cases reported here repre-

sent thyroid failure, as demonstrated by the laboratory findings and response to treatment. Cases of hyperthyroidism and dysthyroidism have been excluded for the sake of clearness and brevity.

#### SOCIAL AND FAMILY HISTORY

*Social History:* The social history of these patients does not yield any new information of value in regard to thyroid failure. It is nearly impossible to make a fair and accurate division as regards nationality, since the mixture of races is so complete. Also, because of the mobility of population, it is impossible to separate patients into significant groups as regards geographical factors, since many individuals have lived in, and outside of, goiter belts for varying periods of their lives. In individual cases, the patient's birthplace and residence may be relevant, but in a large series such factors are not significant. Of this series, 97 per cent gave their nativity as "American." In the majority of these the names were Anglo-Saxon, with a definite minority suggesting Irish or Jewish parentage.

*Sex:* Division as regards sex shows that slightly over one-fourth of our patients are males (see Table I). This agrees with Biedl's (31) figures, but is rather higher than those of Dock (31). All are agreed, however, that hypothyroidism occurs more frequently in women than in men, but that the condition is not extremely rare in the latter. There is no satisfactory explanation of the fact that the female is three or four times more liable to disturbances of thyroid function than the male. It seems possible, however, that this preponderance is due to the alterations in metabolism incident to pregnancy. The female thyroid possesses a potential variation of function not demanded of the male, and this potential variation may cause the lack of stability which seems to distinguish the female from the male gland.

*Age:* Our figures as to age distribution differ slightly from those by Boothby (31) at the Mayo Clinic. Of his 89 cases, 73, or 82 per cent, were between thirty and sixty years of age, while in our 100 cases, only 52 per cent were between those ages, and 41 per cent were less than thirty years old. Possibly the difference may be due to the fact that Boothby's patients were "myxe-

the period of growth. In our experience it is only in the cretins, in whom the lack of thyroid secretion probably exists from birth, that any marked influence of the thyroid upon development is demonstrable. This is in marked contrast to disturbances of pituitary activity, which affect growth as a rule, rather than as an exception.

*Mental Development:* Here again our figures for delayed mental development are certainly less than the truth, but they are significant as indicating that both mental and physical development are delayed or impaired if thyroid activity be depressed, whereas pituitary hypofunction, which also gives rise to delayed growth, has a much less marked effect upon mental development. The practical elimination of cretins from our series adds weight to this statement.

*Sexual Development:* Onset of Puberty. Exact figures for this event can be obtained only from female patients, there being no definite occurrence to mark puberty in a boy as does the appearance of the catamenia in girls. Our figures, therefore, represent only the females in our series. It is courting criticism to attempt to set arbitrary age standards for the normal appearance of menstruation, but for the sake of definite criteria, we have chosen 12 years as the early limit and the fourteenth birthday as the late limit for normal appearance of catamenia. On this basis less than half our female patients certainly began to menstruate during the normal period, and of those whose menarche was abnormal, delay was six times more frequent than precocity. Here again the depressing effect of thyroid hypofunction on development is more clearly apparent, and it is likewise demonstrated that delayed puberty demands careful investigation of the patient's endocrine system (particularly the thyroid and pituitary), if no organic disease can be demonstrated to explain the condition. That thyroid extract will correct the delayed sexual development due to hypothyroidism was beautifully demonstrated by one patient in our clinic. Born a cretin, her condition was early recognized and efficiently treated by Dr. J. J. Thomas of Boston. She came under our observation when she entered the obstetrical ward to be confined, and her past history disclosed the hypothyroid condition. Her menarche was only slightly delayed, her catamenia had been normal, and pre-



sumably she had escaped sterility by the early recognition of her condition and its efficient treatment. If medication is to be effective, it must be instituted during the growth period. It will not suffice to "wait and see" till the patient has passed twenty and then begin thyroid medication. The opportunity has then passed for normal development of the sex organs, and the result of such tardy treatment is almost certainly failure.

TABLE XII

## PREVIOUS ILLNESSES

Mumps .....	47%
Tonsillitis .....	40%
Measles .....	23%
Scarlet Fever.....	23%
Pneumonia .....	15%
Diphtheria .....	12%
Typhoid Fever.....	8%
Emotional Strain.....	6%
Rheumatic Fever.....	3%
Trauma .....	2%
Tuberculosis .....	0%

## PREVIOUS OPERATIONS

Tonsillectomy .....	40%
Appendectomy .....	5%
Cholecystectomy .....	1%
Hysterectomy .....	1%
Thyroidectomy* .....	1%

\*There are a number of cases of hypothyroidism of surgical origin in the larger series.

*Previous Illnesses:* It was possible to demonstrate a definite connection between previous infections and thyroid failure in only scattered instances, and it is our belief that the acute infections are not generally patent factors in the production of hypothyroidism. The incidence of definite and severe chronic tonsillar infection in these patients is, however, prominent enough to suggest that it may be an important etiological factor. Forty per cent of our patients had had repeated severe sore throats and 32 per cent had had tonsillectomy. These figures are higher than those for measles, and nearly as high as those for mumps—both extremely common infections. The further fact that physical examination showed that in 32 per cent of our series the tonsils had been removed and that in an additional 24 per cent

they were definitely infected is significant of a not improbable connection between chronic tonsillar infection and depression of thyroid function. It has also been our experience that the removal of infected tonsils is a necessary preliminary step in the successful treatment of hypothyroidism. In several instances no benefit was obtained from thyroid extract pushed to the point of mild toxic symptoms before tonsillectomy, while the removal of the focal infection was followed by rapid response to a smaller dosage. It is no longer debatable that focal infection has a profound depressant effect upon bodily nutrition and function. How it produces this effect has never been determined, but it seems possible that it may be through the endocrine system and, more particularly, through a direct depression of thyroid or pituitary function.

TABLE XIII

## DURATION OF ILLNESS

Less than 6 months.....	4%
Between 6 and 12 months.....	5%
Between 1 and 2 years.....	20%
Between 2 and 3 years.....	11%
Between 3 and 4 years.....	12%
Between 4 and 5 years.....	6%
Between 5 and 10 years.....	11%
Between 10 and 15 years.....	11%
Between 15 and 20 years.....	3%
More than 20 years.....	7%
"Always" .....	10%

*Duration of Illness:* The striking feature in the table showing the duration of thyroid failure in our series of patients is the long existence of the condition before it was recognized, a feature commented on by Blumer, Janney and others. To a certain extent the failure to make the diagnosis depends upon the insidious onset of the disease, and the lack of definite physical signs to account for the symptoms. In our opinion there is, however, a still stronger reason for the failure of physicians to recognize hypothyroidism. This lies in the general impression, derived from the name applied by Ord to the condition described by Gull, that there can be no really significant depression of thyroid function without the presence of demonstrable myx-

## TABLE XIV

## PRESENT ILLNESS

Patient reported as a

*Symptom:*

	Chief Complaint	Definite Symptom
<i>Menstrual disturbance...</i>	5%	54%
Exhaustion .....	59%	80%
Depression .....	3%	29%
Irritability .....	...	30%
Instability .....	5%	5%
Underweight .....	2%	32%*
Overweight .....	8%	21%*
Goiter .....	7%	14%
Deafness .....	5%	15%
Vertigo .....	4%	36%
Headache .....	8%	46%
Failing vision.....	1%	10%
Paræsthesias .....	4%	24%†
Insomnia .....	1%	16%
Appetite± .....	...	53%
Indigestion .....	3%	25%
Vomiting .....	1%	22%
Constipation .....	3	52%
Sterility .....	2%	39%‡
Impotence .....	7%	11%§
Menstrual disturbance...	5%	54%
Diminished libido.....	3%	33%
Dyspnoæ .....	1%	28%
Palpitation .....	...	22%
Loss of hair.....	2%	30%

## ADDITIONAL

Skin eruptions.....	12%
Diminished perspiration.....	40%
Hypothermia .....	41%
Marked change in weight.....	61%
Personality changes.....	63%
Loss of memory.....	7%
Urinary symptoms.....	14%

\*Observed by measurement.

†Five cases severe.

‡Of 61 married.

§Males = 27.

dema. Therefore the possible existence of hypothyroidism never occurs to the average physician when myxedema is not demonstrable. In a previous paper (33) one of us has called attention to the fact that in a series of forty cases there was no significant difference in basal rate between those cases that showed myxedema and those that did not. The difference between the two groups lay in the ages and in the presence or absence of arteriosclerosis as determined by physical examinations, blood pressure determinations, renal function tests, and urinalysis. It was pointed out that arteriosclerosis was practically the rule in patients with myxedema, and was very rare in those who did not exhibit this condition. Our present series confirms the earlier findings and gives added support to the thesis that while there is no myxedema without marked hypothyroidism, there may be marked thyroid incompetence without myxedema, just as there may be marked renal incompetence without edema. If this be the case, it would be well to drop the use of the term myxedema as synonymous with hypothyroidism, since it seems to inhibit the early diagnosis of that condition.

*Presenting Symptom:* Reference to the chart brings out the fact that while the chief complaints of patients with hypothyroidism are many and varied, the outstanding symptom is general subefficient bodily performance, termed variously "exhaustion," "lack of endurance," "chronic fatigue," or "weakness." This symptom is, of course, the expression of the depressed metabolic activity incident to thyroid hypofunction, and is not due to organic change demonstrable by physical examination. Superimposed upon this expression of abnormal metabolism are a varied assortment of special complaints, indicating the effect of depressed thyroid activity upon practically all the various "systems" that compose the body. Prominent among them stands the nervous system, and because of the prominence of symptoms referable to it, many patients with hypothyroidism have had to carry for years the added handicap of a diagnosis of neurasthenia. It is true that neurasthenia, in its literal meaning is present, but before the term is applied to a patient in its medical sense, hypothyroidism as a possible basis for or aggravating factor of the neurasthenia, must be carefully considered. The tests which prove its presence or absence are so simple that

there is no justification for not applying them. The difficulty in the diagnosis of hypothyroidism lies not in the lack of a certain method of establishing it, but in the failure of the physician to consider it as a possibility in any given instance.

Whenever a patient complains of chronic fatigue or weakness, plus one or more of the symptoms enumerated in Table XIV, and physical examination fails to disclose organic disorder sufficient to explain the symptoms, that patient deserves such tests as are necessary to establish the presence or absence of thyroid or other endocrine hypofunction.

To do this, one measurement of the basal metabolic rate is not enough. There are other conditions that will depress basal metabolism, and these must often be eliminated by a combination of tests sufficient to embrace all the possibilities. As a rule, however, the symptoms enumerated, the absence of organic involvement, the presence of bradycardia, hypotension, hypothermia, changes in personality, malnutrition and abnormal weight, and the demonstration of a basal metabolic rate, properly determined, of —20 per cent or more, with an approximately normal sugar tolerance, is sufficient to establish the diagnosis and eliminate so-called neurasthenia.

*Weight:* This feature has already been thoroughly analyzed and deserves mention here only to emphasize the fact that underweight does not argue against hypothyroidism.

*Loss of Energy:* While this symptom was the chief complaint of only 59 per cent of our series of patients, it occupied a prominent place in the histories of eight out of every ten. It was variously described, but could always be translated into an expression of the inability of the patient to live a normal existence because of lack of energy to meet normal demands. This realization of subefficiency often results in the development of an "inferiority complex" and depression or hostility toward the world in general.

*Psychoses:* Definite psychosis was present in four of our patients, and in all was of the manic depressive type, the depressed phase being much the more prominent and of longer duration. Two of the four had attempted suicide; the other two had seriously contemplated it. All of them complained bitterly of their inefficiency and their inability to enjoy life. Two of the four have responded satisfactorily to thyroid medication, one

seems possible that other factors may be operative. These will be considered below. The constipation is of the atonic type, is aggravated by a diet rich in roughage, and is resistant to treatment by cathartics. It responds readily to thyroid extract.

*Biliary Tract:* Because of the prominence of vomiting, indigestion, and jaundice in our patients (see Table XIV) it seemed worthwhile to study the digestive tract by means of barium meals and radiography, Graham test, and duodenal lavage in a number of cases. The results of this investigation appear in Table XV.

TABLE XV

## RELATIVE INCIDENCE OF LIVER AND GALL BLADDER DISEASE

Diagnostic Evidence	Not Endocrine			
	Thyroid	Long Form	Short Form	Pituitary
<i>Established</i>				
Liver Function				
+	7	12	2	4
++	7	9	1	3
+++	8	7	5	0
Graham .....	1	4	2	1
Operation .....	2	0	0	0
Jaundice (current)....	1	0	0	0
Total.....	26	32	10	8
<i>Probable</i>				
History				
Previous jaundice...	5	3	1	0
Miscellaneous .....	3	0	2	0
Physical Examination				
Enlarged liver.....	2	1	0	0
Tenderness .....	3	0	0	0
Miscellaneous Findings	0	0	2*	0
Total.....	13	4	5	0
Grand total...	39	36	15	8

Comparison has been made between four series of one hundred consecutive cases each, exhibiting respectively thyroid and pituitary disease, and non-endocrine disorders as determined by

\*One case of profound secondary anaemia without determined cause, one case showing duodenal pathology by radiography.

the "Long Form" and "Short Form" studies. The choice of the two latter depends upon the fact that because of certain studies now under way many cases are received selectively for the longer investigation in which a liver (or gall bladder) element is patent before admission. The "Short Form" group is much more representatively a cross section of the general endocrine service. Positive evidences of involvement of liver, gall bladder or both derive from the duodenal function test (McClure), positive Graham test, history of recent cholecystectomy or current jaundice. The probable evidences lie in the facts of the past history, the results of physical examination or other suggestive observations. While but single defining evidences are reported in the table, it is to be understood that the thorough general study adds numerous supporting observations. For example, a number of the positive liver function cases gave positive Graham tests, icteric indices, etc., as well as yet other positive indications.\*. Reverting to the table, it is patent that liver or gall bladder disease is from three to five times as common in thyroid as in pituitary disease, and more than twice as frequent as in a typical group of non-endocrine complaints. The relative parity of incidence in the "Long Form" series of non-endocrine disorders derives in part, as noted above, from the fact that this group selectively contains a number of liver cases admitted for that study.

*Biliary Function:* From the tabulation it is apparent that disturbance of biliary function frequently complicates hypothyroidism. This is of possible importance in explaining the apparently conflicting findings in regard to sugar tolerance in certain patients. If the sugar tolerance suggests disturbed pituitary function, and all other findings are more consistent with hypothyroidism, determination of the biliary function by appropriate methods will often eliminate the apparent conflict.

Whether or not hypothyroidism and disturbances of the biliary tract are causally interrelated, we cannot state from the evidence at hand. It may be, however, that a diseased gall

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\*It may not be impossible here to state that in our opinion, the duodenal function test gives primary information about the level of liver function, while the Graham test, naturally, deals with the gall bladder. With a positive Graham, the function test is usually positive also, but a negative Graham test frequently occurs with a positive liver function test. An inference tentatively offered and awaiting confirmation by further study is that gall bladder disease is usually associated with liver dysfunction, but that the converse is by no means of as frequent occurrence.

bladder furnishes the focus of infection which is the etiological factor in the depression of thyroid function in a given case, and it also seems possible that sluggish biliary function due to thyroid failure may prepare the way for various liver disturbances. The question is being intensively studied in the Clinic, and final conclusions will be reported when sufficient material is available.

*Reproductive System:* A prominent symptom in our patients was disturbance of menstrual function, not dependent on pelvic disease. The type of disturbance was characteristic. Complete amenorrhea, so common in pituitary hypofunction, was rare. Nor does the gradual lengthening of the intermenstrual interval and diminution of duration and amount of flow, likewise characteristic of that condition, occur so frequently in this series of patients. In hypothyroidism the characteristic menstrual disturbance may be characterized as loss of control. Menorrhagia is more common than diminished flow, and the intermenstrual interval becomes markedly disturbed. It may vary from ten days to three months in any given patient. Pain at onset of menstruation occurred in a few of our patients in whom the periods had never become normally established, but it is so uncommon in hypothyroidism that its presence should always suggest possible pelvic involvement.

*Sterility* was present in 39 per cent of our married patients. It was not always possible to determine, in this series, whether the responsibility lay with the patient or the mate, but a special investigation of sterility which we are now carrying out confirms our impression that hypothyroidism may be the sole factor in the production of a sterile marriage, if it exists in either male or female. There are in this series examples of both male and female sterility associated with hypothyroidism, and overcome by proper thyroid medication. One male patient had been married three years, no barrier to pregnancy could be demonstrated in his wife, and, except for lack of energy, he considered himself in perfect health. The full protocol is given later. His physical examination showed no myxedema present. His basal rate was —25 per cent. He was put on thyroid extract June 16; his basal metabolism was normal on (or before) August 18. His wife had a normal menstrual period August 5-9, but the next



period was missed and all the normal signs and symptoms of pregnancy developed. She was delivered, at full term, of a normal babe. It is an important fact in this case that the husband showed spermatozoa of normal number and motility in the condom specimen, and that many of them were dead in the post-coital specimen. Apparently the sterility was due to low vitality of the spermatozoa, which could not survive long enough to meet and penetrate the ovum. As a corollary, a normal condom specimen cannot be accepted as positive proof of potency in the male.

In the females, sterility was as a rule due to failure of conception, and was characteristically accompanied by diminished libido. In one patient this amounted to absolute frigidity, although she had had before the onset of the hypothyroidism normal libido and fertility. In certain cases, however, the sterility is due to repeated miscarriage. An example of this is found in one patient in the series who, after the birth of her first baby, had a severe streptococcus infection of the throat. Thereafter she became easily fatigable and felt "generally below par." She became pregnant three times, but in each instance miscarried without known cause at the end of the third month. Physical examination showed some evidences of malnutrition, low blood pressure, sub-normal temperature, and slow pulse. Her basal rate was —22 per cent. She was given thyroid extract in amounts sufficient to normalize the basal rate. She is now eight months pregnant, and no miscarriage has threatened.

It seems fair to postulate that normal thyroid function in both partners is necessary for a fertile mating. Various explanations of the manner in which thyroid failure operates to destroy fertility have been advanced, most of them involving some subtle and specific interrelation between thyroid and gonad function. Such a theory seems to us unnecessarily complicated and lacking in proof. Sterility, diminished libido and menstrual disturbances are common symptoms of any disease which seriously interferes with bodily nutrition, and we believe that it is by reason of such interference that thyroid hypofunction operates to produce the symptoms referable to the reproductive organs.

*Impotence:* Among our male patients impotence, relieved by thyroid medication, was present in three instances. It is

hard to get accurate information about this symptom, and it is probably more common than our figures indicate. Like sterility, it is simply one evidence of the malnutrition due to the disturbed thyroid function. Its importance lies in the fact that the impotence is generally ascribed to gonad failure, in the absence of other demonstrable cause, and the patient treated on that basis, with generally disappointing results. In our experience primary gonad failure, especially as a cause for impotence or frigidity, is a much rarer condition than thyroid or pituitary hypofunction.

*Skin and Appendages:* The value of the skin as an index of nutrition, is too often overlooked in these days of instruments of precision. This is especially true in regard to diseases of metabolism. That the skin is profoundly affected by depression of thyroid activity is indicated by the frequency with which complaints regarding its condition appear in the patients' histories (see Tables XIV and XVI). Dry, cold skin was present in one-half the series, loss of hair in one-third, thickening and scalliness in 10 and 7 per cent, respectively, and skin eruptions, usually eczematous, in 12 per cent. There is, in these patients, a typical pallid, lifeless appearance of the skin, hair and nails which should always suggest to the examiner disturbed metabolism in general and thyroid hypofunction in particular, especially if anæmia be absent or slight. It must be emphasized, however, that these symptoms are suggestive evidence only and demand much corroborative evidence before they can be regarded as diagnostic of hypothyroidism. It is perhaps noteworthy that myxedema was demonstrable in only 10 per cent of our cases, showing how frequently marked depression of thyroid function exists without this so-called pathognomonic symptom.

However suggestive of hypothyroidism the patient's history may be, a careful and complete examination is essential for two reasons. First, it serves to detect or eliminate organic disease as a basis for the symptoms. If organic disease be demonstrable, consideration of endocrine disturbances should be postponed until it has been eliminated or evaluated. Second, a careful physical examination will bring to light certain findings which in connection with the symptoms should establish a suspicion of metabolic disturbance strong enough to demand investigation of the patient's level of functional performance.

*General Nutrition:* Among the physical findings referred to are the various evidences of malnutrition, such as abnormal weight, either above or below the normal. A reference to Table XVI shows how common these symptoms are in patients with hypothyroidism. Evidence of poor general nutrition was present in 78 per cent of our patients, and the skin was credited with

TABLE XVI  
PHYSICAL EXAMINATION

Skeletal development, over.....	3%
Skeletal development, under.....	4%
More than 10% overweight.....	32%
More than 10% underweight.....	21%
Nutrition, fair .....	27%
Nutrition, poor .....	51%
Skin, dry and cold.....	50%
Skin, dry and scaly.....	10%
Skin, thick .....	7%
Skin, myxedematous .....	10%
Malar flush.....	18%
Hair, scanty .....	30%
Hair, hypertrichosis .....	3%
Hair, coarse and dry.....	28%
Tonsils, absent .....	40%
Tonsils, infected .....	24%
Thyroid, enlarged .....	21%
Heart, enlarged .....	4%
Heart, faint sounds .....	31%
Heart, murmurs .....	6%
Heart, low voltage (cardiogram).....	46%*
Arteriosclerosis .....	16%
Hypertension .....	10%
Hypotension, systolic < 100 mm.....	26%
Hypotension, diastolic < 60 mm.....	12%
Hypotension, total .....	69%
Pulse rate, above 80.....	4%†
Pulse rate, below 70.....	66%†

\*Only 13 cases examined in this series.

†In substantial agreement with the larger series.

being normal in only 33 per cent. Dryness was its characteristic departure from health, but thickening, scaling, myxedematous infiltration and eruptions of which eczema was the commonest, were often combined with the dryness. The skin was cold to the touch in half the patients.

*Hair:* The hair is apparently more resistant to the effects of hypothyroidism than is the skin, as it was judged to be normal in 54 per cent of our series. It was termed "thin" and "scanty" in about one-quarter of the patients; coarse, dry and lifeless in an equal number. Alopecia areata was prominent in one patient, complete alopecia was present in two. Excessive hair growth is a rare finding, in contradistinction to certain of the other endocrine disorders.

*Focal Infection:* As has been already pointed out, the incidence of absent or infected tonsils is extremely high in our patients, the former condition existing in 40 per cent, the latter in 24 per cent. In only 36 per cent were apparently normal tonsils present. These figures are significant, even in these days of enthusiastic tonsillectomy.

*Thyroid Gland:* Goitre was present in 21 per cent of our patients. In all, it was apparently due to simple enlargement. The importance of the finding lies in its negative value in ruling out hypofunction of the thyroid. We have seen goiter, tremor and tachycardia all present in a patient with myxedema, existing as residua of a pre-existing thyrotoxicosis.

*Heart:* Convincing evidence of cardiac enlargement was present in only four of our patients, and in none was the enlargement such as Fahr (35) describes as the typical "myxedema" heart.

*Murmurs* were also conspicuous by their absence, due not improbably to the lack of muscle tone in many instances. This lack of muscle tone is evidenced by the faintness of the heart sounds in these patients, and by electrocardiographic evidence of low voltage. Faint heart sounds were noted in 31 per cent of our series, low voltage in the electrocardiograms in 46 per cent of those examined. One of us (36) has previously reported the presence of this low voltage in hypothyroidism, and its disappearance under thyroid treatment.

*Irregularities:* No irregularities other than an occasional premature beat were noted in our series.

*Pulse Rate:* Bradycardia is so characteristic of hypothyroidism that the presence of the former should always suggest

the latter. Sixty-six per cent of our patients had pulse rates below 70 per minute, while only 30 per cent had normal rates and 4 per cent accelerated rates. In these last, there was evidence of arteriosclerosis and true myocardial insufficiency. The lowest rate recorded in our series was 43 beats per minute. This patient's heart was apparently normal; certainly there was no heart block present.

*Arteries:* Sclerosis in demonstrable amount was present in 16 per cent of our patients. These included all in whom myxedema was demonstrated. Several of the patients with sclerosis were well below the age at which that condition is usually found.

*Blood Pressure:* Normal blood pressure existed in 21 per cent of the series. Hypertension was demonstrated in 10 per cent, accompanying arteriosclerosis and myxedema. Hypotension was recorded in 69 per cent of patients. If there be any error in measurements, it is like that of basal metabolism, practically always on the high side, so that our figures do not exaggerate the incidence of hypotension in hypothyroidism. Twenty-six of our patients registered a systolic pressure of less than 100, the minimum being 80, and twelve had a diastolic pressure under 60, the minimum being 45. That the hypotension is due to the thyroid depression is proved by the return of the blood pressure to normal in these patients under proper medication. It is not necessary to drag the adrenals into the picture to explain the hypotension.

*The Cardio-Renal System:* For many years it has been recognized that the typical myxedemic is prone to show evidences of degenerative changes in heart, blood vessels and kidneys. Our findings in this respect have already been presented and commented upon (33), but it seems necessary to risk repetition in order to make clear our opinion concerning the role played by cardio-renal insufficiency in thyroid hypofunction, and especially in the myxedemic form.

The majority of our patients showed no myxedema, and no definite evidence of cardio-renal disease. In a small fraction, however, myxedema was demonstrable, and in these patients certain evidence of markedly impaired circulatory and renal function, similar to that found in chronic nephritis was present. One

or more of the following findings existed in every case of myxedema: albuminuria, with or without casts; nitrogen retention, as shown by the chemical examination of the blood; arteriosclerosis, hypertension, enlarged heart, or electrocardiographic findings similar to those found in myocardial degeneration. These findings we have grouped under the term "pseudo-nephritis," since they differ from true nephritis in that they are, with the exception of arteriosclerosis, and in some instances hypertension, amenable to treatment with thyroid extract. One of us (33, 37) has already pointed out the close association of this "pseudo-nephritis" with myxedema, and has expressed the belief that the latter is dependent upon the former. Until contemplated animal experimentation has furnished further evidence, we cannot regard the thesis as proven, but we wish here to emphasize the fact that evidences of cardio-renal depression or degeneration are far more common in the myxedemic than in the non-myxedemic group of patients. That the latter group should be regarded as "atypical" is, we believe, due to misconception. The fact that patients in this group are markedly underweight does not argue against this belief, for underweight is well known to exist in the most severe of all thyroid depressions, "cachexia thyropriva." The effect of normal thyroid function upon body weight is to keep it normal; in the absence of such normal thyroid activity the weight may become abnormal by either increasing or decreasing. The factors that determine the direction of its departure from normal are as yet unknown. The myxedemic patient then should be regarded as one in whom circulatory or renal insufficiency, or both, have developed on the basis of a thyroid hypofunction, giving rise to a "pseudo-nephritic" condition, but may have an equally severe depression of thyroid function.

*Dysthyroidism* is the term which we believe is better applied to atypical cases of thyroid hypofunction, since these patients usually exhibit symptoms of both "hypo-" and "hyper-activity" of the gland. They represent, in our belief, individuals who are examined while a previous over-activity is swinging to the under-active level, which is not infrequently its final stage. During this period of transition, certain symptoms due to the previous "hyperactivity" tend to persist longer than others, so that there

exists an apparently paradoxical situation in which nervousness and tachycardia, for example, coexist with hypometabolism and other definite signs of thyroid hypofunction. Eventually such patients either become normal, or, more often, reach a definitely hypofunctional level. The interest in the condition lies in the fact that it explains some of the apparently contradictory findings in certain cases, and that it raises a question as to the advisability of immediate operation, and its extent, in mild cases of thyrotoxicosis. Our own belief is that in the absence of symptoms of cardiac embarrassment such patients should be kept under close supervision until the transition stage is past, and that the type and extent of treatment necessary can then be logically determined. If such a course is pursued, frequent determinations of the basal rate are essential, since the pulse rate, which falls far more slowly, cannot be relied on to give evidence of diminishing thyroid activity. The trend of weight and blood pressure are also important guides.

From the clinical point of view, there are many objections to regarding the estimation of the basal metabolism as a perfectly reliable method of diagnosis of, and progress in, thyroid disturbances. If it be really the basal metabolic rate which is determined, the importance of the first and subsequent readings can hardly be overestimated, but unless the operator understands thoroughly the many factors which may influence the readings, a true rate will not be obtained. We have seen, in this Clinic, a difference between the initial and final determinations of an untreated patient's basal rate amounting to 107 per cent, and varying from an abnormally high to an abnormally low value, without apparent change in the conditions of the test, and due solely to emotional factors which are often difficult of detection. We believe therefore that the basal metabolic rate alone is not a reliable criterion of thyroid activity, and that in the more obscure cases it must be supplemented by the patient's history, physical examination, and a group of other tests and examinations such as are reported in this paper.

In addition to the type of dysthyroidism described above, there is reported in the protocols below a case representative of a small group showing another class of disturbance. In them the basal rate is not altered to a degree comparable to the evident symptoms of toxicity, but the sugar tolerance, usually only

slightly altered in thyroid disturbances, is markedly affected. The theoretical significance of these findings is discussed below. They are mentioned here to show that the basal metabolic rate cannot safely be accepted as the sole criterion of the level of thyroid function.

## PART III—CASE PROTOCOLS

TABLE XVII

Case Number..	Gall Bladder			Psychoses		
	B-467	B-480	B-845	B-875	B-528	B-35
Diagnosis.....	—	—	—	*	—	—
Sex.....	M	F	M	F	M	F
Age..... (yrs.)	31	52	37	32	61	41
Height..... (cm.)	180	163	173	171	177	165
Weight..... (kgm.)	58.7	91.2	18.6	80.2	92.4	68.7
Weight Deviation (%)	-25	+45	-33	+32	+26	+15
Lung Volume Deviation (%)	+6	-52	-27	-12	-14	-46
Basal Rate Deviation. (%)	-29	-36	-33	-32	-29	-50
Blood Pressure. (mm.)	104/60	130/70	116/SS	110/70	146/90	104/70
Pulse..... (per min.)	16	18	56	60	64	71
Temperature.... (deg. F.)	97.4	98.0	98.6	97.8	97.8	95.4
Alveolar CO <sub>2</sub> ... (mm.)	11	43	43	43	35	33
Urine Volume. (cc.)	600	1290	1120	850	790	990
Spec. Grav. . . .	1.024	1.013	1.020	1.019	1.024	1.010
Albumin.....	0	+	0	0	0	+
Casts.....	0	0	0	0	0	0
Sugar.....	0	0	0	0	+	0
Total Nitrogen . . . (gms.)	8.32	7.57	9.30	5.72	5.50	7.62
Residual Nitrogen... (%)	14.5	8.2	6.3	9.0	9.8	6.6
"Urobilinogen".....	0	+	0	0	0	0
Phen. Sulph. Phthal... (%)	50	25	51	19	39	33
Galac. Tol. Deviation. (%)	-33	-83	±0	-25	±0	+25
Non-Protein Nitrogen (mgm.)	40	29	33	26	29	31
Uric Acid ..... (mgm.)	4.1	2.3	1.4	3.3	3.8	3.7
Sugar. . . . . (mgm.)	100	77	82	83	81	71
Haemoglobin..... (%)	95	65	85	95	100	70
Erythrocytes..... (10 <sup>9</sup> )	4.93	3.34	4.14	4.81	4.97	4.33
Leucocytes..... (10 <sup>9</sup> )	5.40	11.9	1.9	6.95	9.60	5.30
Neutrophiles. . . (%)	54	66	45	52	50	62
Lymphocytes..... (%)	35	27	46	40	38	25
Eosinophiles..... (%)	6	2	4	1	2	5
Monocytes . . . (%)	5	5	5	7	9	3
(Basophiles). . . (%)	—	—	—	—	1	5

## THYROID FAILURE WITH GALL BLADDER COMPLICATION

## GROUP I

**CASE B-480.** The patient's chief complaint was of abdominal pain coupled with jaundice. The latter condition was first remarked eighteen months previously and the first attack lasted for about a month, with characteristic stool and urine findings. The jaundice cleared up under medication. Following this, there was a period during which she became very fatiguable and mentally sluggish, with occasional attacks of acute nervous instability. Nearly 20 years before she had been treated for myxedema and from time to time in the interim had had occasional courses of thyroid medication.

**Family History:** Father and one sister died with symptoms similar to those of the patient.

\*See discussion of case.



*Past History:* She reported only measles at the age of 26, severe pneumonia followed by abscess in the right lung at 43, an injury to the spine at 37 which caused temporary paralysis of the left leg. She matured at the age of 9 and had apparently passed through the menopause a few months before admittance. The menstrual history was normal except for menorrhagia prior to the cessation of the periods. She had been married twice, her first experience lasted  $3\frac{1}{2}$  years, with three pregnancies, resulting in one surviving child, a miscarriage at three and a half months, and a child who died at birth. Her second marriage produced one miscarriage four years previously, resulting from a fall while three months pregnant. She had always been constipated; had had a tendency to obesity at times, checked by drastic dietary.

*Physical Examination:* The patient was deeply jaundiced, obese woman, 52 years of age, apparently asthenic and showing a marked mental sluggishness. The sclerae were deeply jaundiced, the few remaining teeth were in poor condition, tonsils were enlarged and cryptic, and there was a slight thyroid enlargement. There was a tenderness on palpation over the entire abdomen, more pronounced over the liver, which was somewhat enlarged; the pubic hair was scanty, skin coarse, dry and deeply pigmented, and large fat deposits were observed on the breast and abdomen. The abdominal reflexes were reported as absent.

*Laboratory Summary:* The patient was 45 per cent above her predicted weight, while the lung volume was less than half that of prediction. She had a basal rate of —36 per cent, with marked bradycardia and substantially normal blood pressure. The urine showed albumin and bile, also a positive "urobilinogen" test. Phthalein elimination was but 25 per cent. The patient's sugar tolerance was greatly lowered. Blood sugar was slightly below normal. Her blood showed a definite secondary anaemia, a slight leucocytosis, and a substantially normal formula.

*Pelvic Examination* showed residua of early child-bearing; a large fundus was freely movable and in good position; the findings were otherwise normal.

The sella by radiography was normal; the lower teeth showed absorption.

*Eye Examination* showed contraction of the form and color fields too marked to permit the delineation of the blind spots.\*

*Neurological Examination* disclosed evidence of multiple neuritis and emotional instability.

*Laryngological Examination* showed hypertrophied and infected tonsils.

An earlier gastro-intestinal radiographic study had demonstrated a cholecystitis.

*Diagnosis:* The patient's condition was obviously thyroid failure coupled with gall bladder disease and a probable dysfunction of the liver. There was also a definite psychoneurosis.

*Comment:* Operation for the gall bladder condition was recommended, to be accompanied and followed by controlled thyroid medication. The operation was successful, a grossly diseased gall bladder being removed. Her jaundice cleared rapidly and she was discharged to continue her thyroid medication. Some two years later she returned

\*Fields of this type have been recorded by one of us in a number of cases of gall bladder and liver disease. Unpublished data. A. W. R.

to the clinic in a much improved condition. Her thyroid medication had been somewhat intermittent and she had increased in weight to 68 per cent above prediction. A duodenal study showed considerable disturbance of biliary function of the liver, a residuum of the earlier gall bladder condition. Her earlier low sugar tolerance had increased to the normal. The eye grounds were still further contracted. Under controlled thyroid medication for a few weeks her basal rate was brought promptly to a normal level. The nervous instability of which she had earlier complained had returned, but a number of social factors had appeared which were undoubtedly of definite significance in producing this result. In spite of this, the mental picture was greatly improved.

**CASE B-467.** The patient's chief complaint was of "bilious attacks," from which he had suffered since childhood. They were characterized by constipation, acid eructation, drowsiness, and dull headaches following meals. There was also a mental dullness of which the patient was acutely conscious, and periods of mental depression. He had attempted to correct the condition by dieting and had eliminated a number of articles of food which he believed to be badly tolerated. Investigation showed that his remaining dietary regimen was entirely inadequate, although containing a maintenance quantity of protein. There has been a gradual loss of weight and a general physical depression.

*Family History:* The father was reported as having had a liver trouble of unknown character and possibly exophthalmic goiter.

*Past History:* The patient was born in South Africa and lived there until the age of 19. He had lived in England since that time, except for two years in the army in France and in the Salonika campaign. He reported most of the minor ailments of childhood, malaria in 1916 with jaundice, and several brief recurrences of this condition until an attack of rheumatic fever in 1917. He had had no malaria since this latter condition, but had had two attacks of jaundice in 1925. He had been subject to asthma since the age of 9, also bronchitis; he had an attack of influenza at the time of the epidemic. He reported a possible protein sensitivity to horse dandruff and to feathers. His appetite was good, but digestion was poor. Among other interdicted articles of food were eggs, cheese, and fats of all kinds. He had used Epsom salts and calomel very freely.

*Physical Examination* showed a very well set up and athletic, but undernourished, Englishman of 31 years of age. There was a yellowish tinge to the skin and the conjunctivæ were yellowish. His abundant black hair was tinged with gray; the teeth showed much dentistry; there was some minor adenopathy in the neck. The heart was normal and there was no tenderness over the gall bladder. The left testicle was undescended. The thyroid was not enlarged. The remaining findings were substantially normal.

*Laboratory Summary:* The patient was 25 per cent under his predicted weight, showed a basal rate of —29 per cent, with low blood pressure, bradycardia, and somewhat subnormal temperature. The scanty urine was free from abnormalities except a high residual nitrogen. The sugar tolerance was somewhat depressed. The blood chemistry gave evidence of some retention. The blood morphology showed a lymphoid blood with a slight eosinophilia, undoubtedly due to his protein sensitivity.

Repeated examination of the blood for plasmodia failed to show them.

*Neurological findings* were normal.

*Abdominal findings* were normal.

*Endermal Tests:* A positive response to egg and doubtful positive to wheat and milk was found; the reaction was negative to a large number of other proteins.

*Radiography:* A gastro-intestinal series was substantially normal. The skull and sinuses were normal. The chest showed increased density at the right apex, with haziness and scattered mottling over the whole lung area. A Graham test by the oral route was negative.

*Duodenal Function Test (McClure):* The patient showed a very marked disturbance of biliary function.

*Audiogram:* Substantially normal hearing was found.

*Stool Examination:* Blood, ova, parasites, and cysts were reported absent.

*Cardiac Examination:* Beyond a short systolic murmur, with the first sound at the apex, a frequent finding in normal individuals, the findings were entirely normal.

*Eye Examination:* Gave normal findings.

*Discussion:* On the basis of the findings given, a diagnosis of hypothyroidism, coupled with a liver dysfunction, was established. Thyroid medication was suggested for the first, and duodenal lavage for the second. Under this treatment the patient's condition rapidly cleared; he gained in weight, the jaundice disappeared, sugar tolerance became normal, and the general laboratory picture showed marked improvement, including a disappearance of the blood chemistry findings suggesting lowered kidney permeability (see pseudonephritis later). Shortly after this study the patient returned to England, and we are advised that he has had one or two relapses of the liver condition, which, however, have yielded to further treatment by lavage.

CASE B-845. The patient's chief complaint was of skin eruption and an inability to digest certain foods. In 1909 he developed a skin disease diagnosed as ichthyosis. The skin became hypertrophic; there was much exfoliation, with a transitory and recurrent erythema. The latter seemed to depend primarily on the use of such foods as fat, fruit, and milk. Milk caused abdominal pain, while fats have produced a yellow color of the skin. High protein diet will also cause the yellow color, but the patient could take liver freely, an interesting point in view of his fat intolerance.

*Family History:* Two grandparents died of cancer, and the mother had been operated upon for gall stones.

*Past History:* The patient reported the minor ailments of childhood, together with pneumonia and diphtheria in early years. Influenza at the time of the epidemic was complicated by an involvement of the antra and ethmoids, which later disappeared without treatment. An appendectomy was performed in 1909, and an exploratory laparotomy in 1917 showed an alleged normal gall bladder. The patient had also been operated upon for tonsilitis, hemorrhoids, and had had several infected teeth extracted. He complained of an occasional unilateral headache, marked optic fatigue, occasional pain in the right ear, and recurrent pharyngitis after the use of milk or cream. Recently he had had attacks of precordial pain, which was aggravated

by the use of thyroid. Tingling and numbness of the hands and feet and some myalgia had been recent developments. For some time past he had had a non-specific prostatitis. He had lost 17 pounds in the six months prior to his admission.

*Physical Examination:* The patient was a well-developed but distinctly emaciated white man, 37 years of age; the face was pallid with a definite lemon-yellow cast; the conjunctivæ were slightly yellowish. There was a moderate deviation of the septum. No thyroid enlargement was present. The heart sounds were indistinct, the beat irregular, with recurrence of several rapid beats which were not typical extrasystoles. There was definite bradycardia and hypotensive blood pressure. The right testicle was somewhat tender and there was possibly tenderness over the gall bladder. Minor inguinal and definite cervical adenopathy was found. The skin was dry, scaly, and hypertrophic. The tendon reflexes were reported as sluggish.

*Laboratory Summary:* The patient was 33 per cent below his predicted weight, the lung volume but slightly below prediction. The basal rate was —33 per cent. The blood pressure recorded at this time was distinctly higher than upon several other observations, but still hypotensive. There was bradycardia. The sugar tolerance was normal; the blood uric acid high. There was a slight secondary anaemia and borderline leukopenia. The blood was lymphoid in type, with a slight relative increase in the eosinophiles.

*Skin Examination:* There was a mild ichthyosis, suggestive of thyroid failure. Several other possibilities were considered and rejected on the ground of other observations.

*Endermal Tests:* The patient reacted positively to several cereals—celery, spinach and peas—and negatively to a large number of common food proteins.

*Cardiac Examination* gave entirely normal findings. The cardiogram showed a slurring of the QRS complex and the contour of the "T" wave in leads II and III was suggestive of possible myocardial impairment, without defining it.

*Neurological Examination* gave substantially normal findings, except for a possible loss in deep sensation over the lower extremities and somewhat diminished reflexes.

*Abdominal Examination* disclosed no abnormalities, failing to confirm the earlier report of tenderness over the gall bladder.

*Eye Examination* showed normal conditions.

*Radiography* of heart, lungs, diaphragm, lumbar spine, hips, pelvis, and skull disclosed no abnormalities.

*Neutral Red Test:* Normal.

*Gastric Examination:* Abundant free hydrochloric acid.

*Endoscopic Examination* showed an enlarged, tender prostate, with involved left seminal vessels and normal bladder.

*Duodenal Function Test* showed marked hepatic disturbance.

*Icteric Index:* 50-75.

*Van den Bergh:* Negative.

*Pancreatic Enzyme Examination* showed normal concentration and activity.

*Laryngological Examination* gave normal findings.

*Microscopic Examination:* Numerous giardia were demonstrated in the duodenal contents.

*Discussion:* The case presented a number of interesting possibilities. Primary anæmia was ruled out by the tests given above and by repeated examinations of the blood, none of which gave any indication of this condition. The normal pancreatic lipase content referred the patient's fat intolerance to the biliary disturbance. The demonstration of the giardias in the duodenal contents (a fact of which the patient had been earlier advised) offered a basis for the patent disturbance of gall bladder and presumptively liver function. In addition there was a definite thyroid failure. It was felt in this case that the invasion of the duodenum by the parasite was probably a starting point for the general condition. Duodenal lavage with substances such as magnesium sulphate, known to be antagonistic to these parasites, was advised. Thyroid medication was also recommended, recognizing, on the basis of past experience that complete correction could be expected only when the parasites had been exterminated and the liver brought back to a normal level of functional activity. Later advices showed some improvement in the condition, but the giardia are still present.

## GROUP II. PSYCHOSES

CASE B-35. The patient's chief complaint was easy fatigability, with lameness in the left knee and general nervousness. The entire picture was dated from the birth of the patient's last child in 1918, five years before the patient was seen. Several earlier medical contacts had ascribed the patient's condition to pelvic disorders and an operation had been advised, which had been refused, however. The patient was in a markedly depressed condition, from which she would emerge into sudden bursts of temper without exciting cause. There were several hallucinations, the whole defining a manic depressive psychosis.

*Family History* was not significant.

*Past History:* The patient reported the minor ailments, scarlet fever and pneumonia in childhood and typhoid fever at the age of 26. A tonsillectomy had been done the year before. She had been subject to head-colds. Her bowels were constipated. Otherwise the history was not remarkable. She had been married for 12 years and had borne three children without miscarriage. The menstrual history was not remarkable beyond brief and somewhat scanty periods.

*Physical Examination:* The patient was a well-developed, somewhat obese white woman, 41 years of age. The skin was very dry and scaly, hypertrophic, and did not pit on pressure. The hair of the head and eyebrows was coarse and somewhat scanty. The palpebral fissures were narrow, the upper and lower eyelids were puffy. The tongue increased in size, but without tremor on extension and not prominently fissured. A few bubbling rales were reported in the region of the bronchi; blood pressure was low, and there was definite bradycardia; the hands were broad, fingers short, the nails were thickened and striated; the facies was typical of myxedema. The patient's mental reaction was very sluggish and the speech thick, possibly as the result of enlarged tongue.

*Laboratory Summary:* The patient was overweight and nearly 50 per cent below predicted lung volume. The basal rate was —50

per cent, the blood pressure low, the pulse normally very slow, though at the time of the reported basal examination it was 71. There was a marked subnormal temperature. The low alveolar carbon dioxide was probably due to the patient's inability to cooperate. The sugar tolerance was slightly increased. Blood sugar was low, and the blood morphology showed a secondary anæmia with a 5 per cent basophilia. An interesting point in connection with this case is recorded in a basal test done during the latter part of the patient's stay. At this time she had developed a slight infection and showed a temperature of 100.8° F. The basal rate at this time was —25 per cent. If we calculated to her usual daily temperature this would correspond to a value around —60 per cent. Another interesting point was found in a series of comparative blood pressure measurements. The first recorded, at a time when the patient was in a tense, nervous condition, was 166/110. Subsequent measurements made under quiet conditions showed an average slightly below that recorded in the table.

*Eye Examination:* The patient showed substantially normal findings, except for slightly enlarged blind spots and cutting of the upper form fields, due to lid droop.

*X-Ray:* Chest and skull were normal.

*Pelvic Examination* gave normal findings.

*Neurological Examination:* There was no evidence of organic nervous lesion. The patient's mental state was ascribed to her glandular condition.

*Discussion:* The presenting data warranted the diagnosis of marked hypothyroidism with myxedema. Thyroid medication was recommended, and this was actively carried out. In the course of a few months the patient showed the usual remarkable results which may be confidently expected from controlled thyroid medication in an uncomplicated case of thyroid failure. A most interesting feature of the case was the complete disappearance of the mental symptoms, which at the end of five years have shown no tendency to return.

**CASE B-528.** The patient's chief complaint was of a recurrent profound mental depression, of which this was the latest attack, the first having appeared some 23 years before. Three years later there was a recurrence which cleared up spontaneously in a few months, and again 14 years later there was a three months' attack. In the preceding year there had been a downward tendency, but the progress had been so slow that it did not become serious until a short time before admission. The last attack had been characterized by an attempt at suicide, the earlier seizures having shown no tendency toward self-destruction.

*Family History:* Beyond a sister with epilepsy, the history was not informative.

*Past History:* The patient reported the usual minor ailments with freedom from any serious disease. He had a slight productive cough apparently arising in a throat irritation. The bowels were regular. There was a question of jaundice many years before. He had been overweight for a number of years.

*Physical Examination:* The patient was a well-developed, obese man of 61 in a state of marked mental depression. His complexion was ruddy, his skin was normal in texture and moisture, the breath was foul. Several teeth were missing and the remainder in only fair condition. The heart and lungs were apparently normal; the

abdomen obese and not tender on palpation; the knee jerks were not elicited.

*Laboratory Summary:* The patient was 26 per cent overweight; he showed a basal rate of —29 per cent; the urine volume somewhat low; the urine contained a trace of sugar. The protein intake was below a maintenance level; the residual nitrogen high. Sugar tolerance was normal. Blood morphology showed a lymphoid type.

*Radiography:* The sella was small; teeth were normal.

*Cardiogram:* Normal.

*Neurological Examination* gave no evidence of organic nerve lesion.

*Eye Examination* disclosed slight irregularity of pupils with yellowish discs and some cutting of the upper form fields due to lip droop.

*Psychiatric Examination* defined a manic depressive psychosis in the depressed phase.

*Discussion:* Beyond the trace of sugar in the urine, which is occasionally observed in uncomplicated mental cases, and which in the present instance is balanced by the normal galactose tolerance, the presenting picture is one of hypothyroidism. Another possible explanation of the sugar anomaly might lie in the record of an earlier jaundice, but this was so many years ago as probably to be devoid of meaning. Thyroid medication was advised and given with apparently complete recovery on the part of the patient. There has been no subsequent evidence of recurrence in the years that have supervened. Too much weight should not be laid on the correction of the mental condition, but it is interesting to note that the normalizing of the physical state coincided with that of the mental. It may, however, be no more than a coincident remission.

CASE B-875. The patient's chief complaint was fatigability. She had suffered from a manic depressive psychosis for a number of years. Her childhood home conditions were unhappy but she evidenced no marked depression until 10 years ago when she divorced her first husband after one year of married life. For the next two years she showed periods of depression in the fall and winter, followed by terms of exaltation in the remaining two seasons. She attempted suicide in 1919 but voluntarily gave up her attempt out of consideration for her family. She was married again 2 years later, an event which involved a marked change of residence. Has had recurrent periods of depression, during one of which she again attempted suicide. She had received a variety of endocrine therapy without result. Her second attempt at suicide followed a three weeks' course of thyroid medication.

*Family History:* Her maternal grandfather committed suicide. The history is otherwise irrelevant.

*Past History:* She had minor ailments, diphtheria and scarlet fever in childhood, jaundice at the age of 7, frequent attacks of tonsilitis and quinsy sore-throat until a tonsil and adenoid operation at the age of 10, which was repeated 12 years later. She has occasional headaches, some tinnitus, and is usually constipated. Her menstrual history shows early onset, marked irregularity, and normal periods. A few years previously she was markedly obese and is still much overweight. She usually loses weight during depressed periods. She has had no children by either marriage.

*Physical Examination:* The patient is a well-developed, obese woman 32 years of age. The hair is fine and abundant and of normal distribution; there is some nasal obstruction; the thyroid is not enlarged; the heart and lungs are normal; she has somewhat low pulse and blood pressure; the remaining findings are normal.

*Laboratory Summary:* The patient is distinctly overweight. Her basal rate is -32 per cent, blood pressure and pulse somewhat low. There is a slight oliguria, somewhat high residual nitrogen, inadequate protein intake, and slightly low phthalein output. The sugar tolerance is slightly depressed. Blood sugar is a low normal. The blood is lymphoid in type.

*Pelvic Examination:* Normal.

*Orthopedic Examination:* The patient shows poor posture; otherwise is substantially normal.

*Radiography* shows prominent clinoids, but no other abnormalities.

*Cardiogram:* Normal.

*Eye Examination* shows yellowish discs, slightly enlarged blind spots.

TABLE XVIII

	Thin Without Myxedema		Sterility		Deafness	
Case Number....	B-44	S-235	S-1013	S-1528	S-107	S-1466
Diagnosis.....	—	—	—	—	—	±
Sex.....	F	F	F	M	M	F
Age..... (yrs.)	41	49	26	34	40	19
Height..... (cm.)	170	167	160	178	163.5	161.5
Weight..... (kgm.)	47 S	66 0	83 2	80 9	60.2	63 0
Weight Deviation.... (%)	-29	-8	-34	+11	+18	±0
Lung Volume Deviation (%)	+6	-32	-12	-3	-6	-10
Basal Rate Deviation. (%)	-32	-31	-26	-26	-22	*-12
Blood Pressure. . . (mm.)	108 90	105 58	102 61	106 68	132/80	110 70
Pulse Rate.... (per min.)	61	54	52	56	72	76
Temperature.. (deg. F.)	97 6	97 2	97 8	97 1	98.9	98.0
Alveolar CO <sub>2</sub> .. (mm.)	31	34	43	39	38	43
Urine Volume. (cc.)	1420	1280	910	1350	1510	760
Spec. Grav....	1.013	1.019	1.025	1.023	1.015	1.029
Albumin.....	0	0	0	0	0	0
Casts.....	0	0	0	0	0	0
Sugar.....	0	0	±	0	0	0
Total Nitrogen . (gmss.)	8.68	10.79	10.70	12.00	9.63	10.91
Residual Nitrogen. (%)	5.4	20.4	11.8	10.0	13.6	11.5
"Urobilinogen".	0	0	0	0	0	0
Phen. Sulph. Phthal. (%)	51	35	58	69	45	35
Galac. Tol. Deviation (%)	+0	±0	—	±0	—	-25
Non-Protein Nitrogen (mgm.)	42	29	32	30	25	32
Uric Acid..... (mgm.)	3 S	2.7	2.8	3.6	3.2	3.0
Sugar... (mgm.)	87	105	100	96	100	93
Haemoglobin.. . (%)	85	95	85	100	90	90
Erythrocytes. (10 <sup>6</sup> )	4.36	4.86	4.37	4.95	5.46	5.36
Leucocytes.... (10 <sup>3</sup> )	6.80	5.70	7.80	5.20	8.20	8.50
Neutrophiles. . (%)	39	41	—	50	61	60
Lymphocytes... (%)	55	50	36	41	34	28
Eosinophiles.... (%)	2	3	1	2	0	0
Monocytes..... (%)	2	5	2	7	5	10
Basophiles..... (%)	2	1	—	—	0	2

\*Transition level.

*Psychiatric Examination* confirms the diagnosis of a manic depressive psychosis, in the depressed phase.

*Discussion:* Again barring the slightly lowered sugar tolerance, the picture is one of uncomplicated thyroid failure. The patient's



history of an earlier attack of jaundice might offer a possible explanation of the sugar anomaly or, as noted above, it may be intrinsic in the mental condition, as we have observed it in a number of such cases which offered no other explanation for the abnormality. This case is still under treatment and the outcome has not been determined.

### GROUP III. AMYXEDEMIC THYROID FAILURE

CASE B-44. The patient's chief complaint was of very severe headaches from which she had suffered since childhood. She usually woke up with them in the early morning. They were completely prostrating, lasted about a day, might come at regular intervals of two or three weeks and again she might be free for two or three months. They were not accompanied by disturbances of vision, but she was often nauseated. A mild glycosuria had been observed on several occasions and the patient found that the headaches were less severe and frequent when under a dietary modification which rendered her sugar free.

*Family History:* Both the father and one sister had similar headaches.

PLATE 1



*Past History:* She reported the minor ailments of childhood, one attack of jaundice, severe tonsillitis, and several accidents not relevant to the present difficulty. She had been underweight for a long time. She developed transitory arthritis with urticaria after a serum injection a year previously. She complained of dyspnoea, of palpitation, and occasionally precordial pain. The respiration rate showed a peculiar anomaly with a deep sighing breath at fairly regular intervals. (See Plate I.) The patient was conscious of this and found it extremely embarrassing. The menstrual history shows a normal onset, regularity with a shortened interval and somewhat profuse flow. She had had intermittent attacks of urinary frequency.

*Physical Examination:* The patient was a poorly developed and nourished woman 41 years of age, with skin smooth and moist, thyroid not enlarged, breasts atrophic, heart and lungs negative, hypo-

tensive blood pressure. The routine neurological examination disclosed only exaggerated knee jerks.

*Laboratory Summary:* The patient was much below her predicted weight. The basal rate was —32 per cent with low blood pressure, somewhat slow pulse and slightly sub-normal temperature. The basal rate as recorded was undoubtedly too high as the patient was slightly restless. That recorded is the lowest of several observations, all of which, however, were below —20 per cent. Alveolar  $\text{CO}_2$  was slightly low but this was probably due to an inability to exhale properly. The urine was normal; nitrogen partition, normal; phthalein test a low borderline normal; sugar tolerance was normal. The blood nitrogen was slightly high; the morphology showed a slight secondary anemia and a lymphoid blood. A provocative urea curve was somewhat low, offering another evidence of lowered kidney permeability.

*Barany Test:* Normal.

*Discussion:* While the patient violated most of the conventional clinical signs of hypothyroidism, the essential features of the laboratory picture could be interpreted only in terms of thyroid failure. She was placed on thyroid extract and in a short time showed a complete clinical cure. Her only relapse of significance during the past 5 years was on one occasion when she went for a number of weeks without medication. Resumption of her medicine produced an immediate correction. A short time after treatment was started a brief check-up examination was made. The patient had gained considerably in weight (this is a constant finding in this type of thyroid failure, the patients being initially underweight). The blood pressure had increased to 120/80, the temperature to  $98.6^\circ$ , the basal rate was normal. The phthalein output showed a definite increase. Non-protein nitrogen of the blood had fallen to 30 mgm., while the uric acid had fallen off a few tenths. All the earlier evidences of lowered kidney permeability had practically disappeared. The blood morphology had improved, the lymphocytes having fallen to 37 per cent. This was one of the early cases of what we have designated a "pseudonephritis," on which comment has been made earlier in the paper.

CASE S-235. The patient's chief complaint was of fatigability which apparently began in childhood. At the age of 11 she began to put on weight, localized chiefly in the legs. This condition had been a serious annoyance and she had made numerous efforts to correct it but without success. The patient had a wide variety of medical contacts, and had been under intermittent glandular therapy with pituitary extract predominating. Four years before she had developed urinary frequency which was ascribed to cystitis. Two years prior to admission she had had an intestinal stasis demonstrated by the radiography. A radical diet with some glandular therapy had produced some subjective improvement. The bowels were markedly sluggish. There was a loss of hair and dry, rough skin. An inhibiting feature was a feeling of mental depression which the patient was not able to combat.

*Family History:* Was irrelevant except for the fact that her relatives were all tall, large people.

*Past History:* She was never strong. She had the usual children's diseases; frequent sore-throats: from 7 until 15 much trouble with running ears. During her school years she found it difficult to concentrate. A tonsillectomy at 30 produced some benefit in the general condition. The catamenial and marital history were negative.

*Physical Examination:* The patient was a fairly developed, poorly nourished woman of 49. The hair was dry and short, the skin dry and rough, the thyroid was not palpable, the blood pressure was hypotensive. The legs were disproportionately large but not edematous. The remaining findings were substantially normal.

*Laboratory Summary:* The patient was 8 per cent underweight, and definitely below predicted lung volume. The basal rate was  $-3\frac{1}{2}$  per cent, with low blood pressure, bradycardia, and sub-normal temperature. The urine was normal except for a very high residual nitrogen. The phthalein output was definitely below normal. The low alveolar CO<sub>2</sub> was probably apparent rather than real. The sugar tolerance was normal. The blood showed a marked lymphocytosis.

*Neurological Examination* showed no abnormalities.

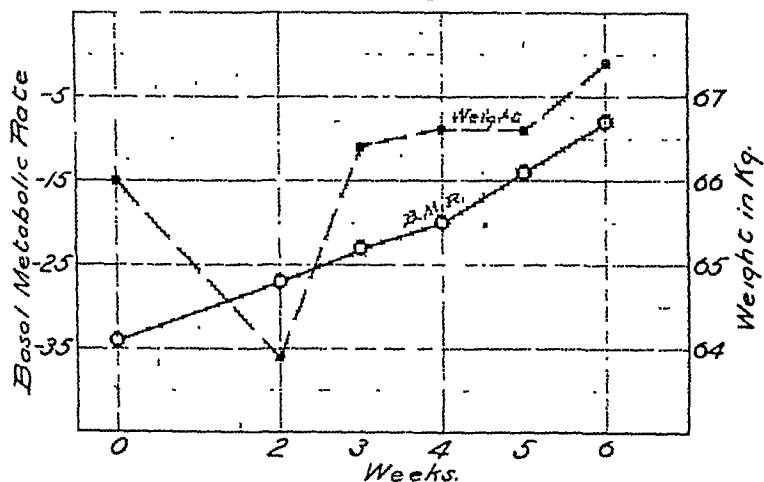
*Barany Test:* Normal.

*Eye Examination* showed slightly enlarged blind spots.

*Radiography* showed a normal sella.

*Discussion:* That the patient presented an endocrine disorder was patent from the facts as obtained. Further, a thyroid failure was the only endocrinopathy in harmony with the data. Thyroid medication was advised, and through the complete cooperation of the patient it was possible to check the progress of the case over a period of six weeks. Certain significant results are given in the accompanying graph. (See Plate II.)

PLATE II



Case S 235 Change in weight and basal rate under thyroid medication in a case of failure.

It will be noted that there was a loss of weight during the first two-week period which promptly recovered, and the patient showed a net gain of 1.4 kgm. in the six weeks' interval. Later observation had shown a re-distribution of weight, the obesity of the legs having become definitely less.

#### GROUP IV. STERILITY.

CASE S-1013. The patient's chief complaint was of sterility, coupled with dysmenorrhea. She had been married for two years without becoming pregnant and without at any time having practiced

contraception. She matured at 11, and the history gave regular periods of somewhat brief duration with scanty flow. There had always been pain, appearing shortly after the flow began and lasting about two days. Numerous clots were passed. She had tried various forms of medication, including ovarian extract, without betterment.

*Family History:* Several cases of malignant neoplasm were recorded; the remaining history was irrelevant.

*Past History:* The patient reported only measles and whooping cough of the minor ailments and none of the more severe conditions. There was a history at the age of 6 of a fall with trauma to the head, which left no apparent after-effects. Two curettage operations had been performed and fifteen months before her hospital entry one fallopian tube had been taken out. The remaining history shows some intermittent gastro-intestinal disturbances, constipation, and a gain of some 20 lbs. within the past two years. She began to become obese at the time of the onset of the catamenia but had been able to control it in some measure by diet.

*Physical Examination:* The patient was a well-developed woman, 26 years old, exhibiting a generally distributed obesity. There was a symmetrical thyroid enlargement of moderate amount, a slight tenderness over McBurney's point, and certain postural defects, probably ascribable to obesity. The findings were otherwise normal.

*Laboratory Summary:* The patient was 34 per cent above her predicted weight. The basal rate, under fairly satisfactory conditions, was 26 per cent below prediction, the lung volume was but slightly impaired, the blood pressure was low with bradycardia. The urine volume was somewhat low with a questionable positive test for sugar. The residual nitrogen fraction was distinctly above the normal; the blood was lymphoid in type.

*Radiography* showed a normal skull.

*Pelvic Examination* gave no evidence of pathology.

*Discussion:* The picture defined by the laboratory tests was considered to be fairly typical. A diagnosis of thyroid failure was offered and thyroid medication instituted. A subsequent report from the patient's physician was to the effect that shortly after beginning treatment the patient had conceived and borne a normal child.

CASE S-1528. This case is particularly interesting. It is one of the series of sterility studies which the authors and their colleagues have been conducting for some time. The work in general will be described elsewhere in the near future. It is enough to say here that it involves a very thorough study of both partners to the marriage, one phase of which deals with possible endocrine factors.

The patient's chief complaint was the sterility of his marriage, as in the course of three years his wife had failed to conceive. The patient himself was somewhat asthenic and had been so for something over a year. The removal of an abscessed tooth during this period produced only a slight temporary relief from this symptom.

*Family History* was not significant.

*Past History:* The patient reported the minor ailments of childhood, scarlet fever, lobar pneumonia, and a questionable attack of small-pox in childhood. He had a mild attack of influenza at the time of the epidemic. There had been a moderate loss of hair. He was

both astigmatic and myopic and showed a susceptibility to rhinitis. He complained of coldness of the extremities and reported some dermatographia.

*Physical Examination* showed a well nourished, slightly obese white male, 34 years of age. The hair was thin, and there was a partial alopecia. The remaining examination gave substantially normal findings.

*Laboratory Summary:* The patient was slightly above predicted weight, had a normal lung capacity and a basal rate of —26 per cent with low blood pressure, slow pulse, and a slightly sub-normal temperature. The urine was normal except for a high residual fraction in the nitrogen partition. The sugar tolerance was normal: the blood, lymphoid in type. In the sterility study the wife was eliminated as a contributing factor.

*Genitourinary Study:* No physical abnormalities were found, while the condom specimen was normal in regard to the number, motility, and morphology of the spermatozoa. A post-coital examination showed the presence of spermatozoa, about half of which were dead or non-motile.

*Cardiogram:* Normal.

*Discussion:* The laboratory examination demonstrated a clear-cut thyroid failure in the husband. The chief interesting feature lies in the fact that on the basis of the condom specimen the husband would have been eliminated as a factor in the sterility equation under the ordinary conditions of practice. The patient was placed on thyroid medication the wife conceived inside of two months, and after an uneventful pregnancy was delivered of a normal child.

#### GROUP V. DEAFNESS.

*CASE S-407.* The patient's chief complaint was of a progressive deafness which had lowered his aural acuity in the left ear so that only loud noises could be apprehended. In the right ear the hearing was poor but the impairment less pronounced. The condition began at the age of 30 involving first the left ear only. He had been troubled with tinnitus.

*Family History:* The mother suffered from the same complaint. The remaining family history was irrelevant, except for one aunt who was insane.

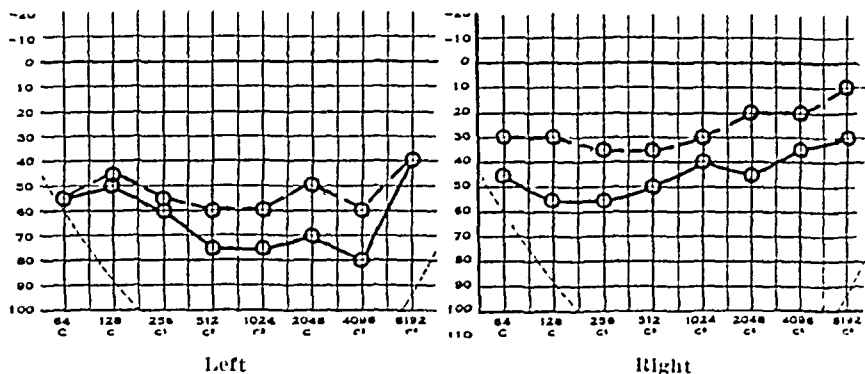
*Past History:* The patient had the usual childhood ailments but had been perfectly well during his adult years.

*Physical Examination:* The patient was a well-developed male of 40 with an obesity of general distribution; the muscles were flabby, and the mental reaction sluggish. Both ears exhibited deafness which in the left was more pronounced. The remaining findings were normal.

*Laboratory Summary:* The patient was overweight. His basal rate of —22 per cent derived from a not altogether satisfactory test. The true rate was probably somewhat lower. There was a high residual nitrogen in the urine and a slight relative lymphocytosis.

*Audiogram (see Plate)* showed marked loss of hearing in both ears, more pronounced in the left.

## PLATE III



Case S-107. Audiograms showing improvement after 6 months of thyroid medication.

*Discussion:* It was not possible to make as thorough a study on this case as was desired, but a tentative diagnosis of thyroid failure was offered as being the most probable condition. The patient responded well to thyroid medication, and six months later there had been a definite improvement in hearing, as shown by the second audiogram curves (see Plate).

**CASE S-1466.** The patient's chief complaint was of deafness in the right ear which had begun about a year before without any apparent cause. It had been progressive, although at the time of the examination it was felt to be at a standstill. She experienced tinnitus and exhibited paracusis.

*Family History:* There was a marked history of cancer on the paternal side.

*Past History:* The patient recorded minor ailments, an attack of influenza during the epidemic, followed by arthritis, for which she was under treatment. Four years previously she had been operated on for a felon and in the preceding October an appendectomy had been performed. She complained of dyspnoea, some palpitation, and intermittent constipation. Her menstrual history was not remarkable. For some time the patient had been very fatigable. She had gained slightly in weight. With somewhat unusual self-perspective she stated that she had become very irritable.

*Physical Examination:* The patient was a well-developed, well-nourished girl of 19. During the examination there was a constant slight movement of hands and feet, occasionally of the body and extremities. The eyes were normal; there was no tremor of the tongue; the thyroid was slightly enlarged. She exhibited some tenderness near the appendectomy scar. There was no tremor of the hands but the fingernails were bitten off. The skin was dry and on the legs showed fine scaling.

*Laboratory Summary:* The patient's weight agreed with prediction. The basal rate was  $-12$  per cent, under fairly satisfactory conditions (v. s.). The blood pressure was somewhat low, the urine small in volume, concentrated and containing an abnormally high residual nitrogen fraction. The sugar tolerance was slightly depressed. Blood chemistry and morphology were normal.

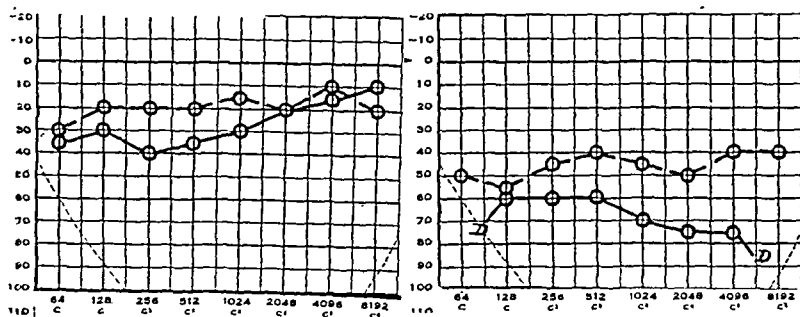
*Neurological Examination:* No evidence of organic nervous disorder was found.

*Pelvic Examination* gave normal findings.

*Cardiogram*: Normal.

*Audiogram* (see Plate) showed marked loss of hearing in the right ear and some loss in the left.

PLATE IV



Left

Right

Case S-1466. Audiograms showing improvement after 8 months of thyroid medication.

*Discussion*: The patient seemingly presented a thyroid dysfunction, not impossibly of the transition type. The basal rate of —12 per cent was felt to be certainly above the truth, and the cautious exhibition of thyroid medication was recommended. Eight months later the patient returned for a test of the aural acuity, and the audiogram (see Plate) showed some improvement in the left ear and marked betterment in the right.

TABLE XIX

	Familial Influence			
Case Number	S-1371	S-1456	S-1520	S-1438
Sex	M	M	F	M
Age (yrs.)	54	19	18	15
Height (cm.)	170	182.5	166.5	171.6
Weight (kgm.)	57.5	60.5	53.2	56.8
Weight Deviation (%)	+1	-15	-12	-1
Lung Volume Deviation (%)	-13	-3	-9	+2
Basal Rate Deviation (%)	(-10)	-31	-30	-21
Blood Pressure (mm.)	138/86	108/64	102/70	108/66
Pulse Rate (per min.)	54	67	60	62
Temperature (deg. F.)	97.7	97.0	98.4	97.8
Alveolar CO <sub>2</sub> (mm.)	57	48	41	42
Urine Volume (cc.)	1510	1280	1250	560
Spec. Grav.	1.015	1.024	1.015	1.026
Albumin	+	0	+	0
Casts	0	0	0	0
Sugar	0	0	0	+
Total Nitrogen (gms.)	9.70	11.91	7.38	7.20
Residual Nitrogen (%)	5.7	11.7	4.7	11.9
P. S. P. (2 hours) (%)	37	36	59	57
Galactose—Normal (gms.)	30	30	40	30
Observed (gms.)	30	not	not	not
Deviation (%)	±0	done	done	done
Blood—N. P. Nitrogen (mgm.)	32	30	30	27
Uric Acid (mgm.)	2.8	3.3	3.8	3.4
Sugar (mgm.)	87	87	96	87
Haemoglobin (%)	80	85	75	95
Erythrocytes (10 <sup>6</sup> )	4.00	5.59	4.29	4.93
Leucocytes (10 <sup>4</sup> )	5.00	5.20	9.03	5.00
Neutrophils (%)	52	56	62	56
Lymphocytes (%)	42	38	35	35
Eosinophiles (%)	0	0	1	1
Monocytes (%)	5	5	2	7
Misc. (%)	1	1	0	1

## GROUP VI. FAMILIAL INFLUENCE.

While it is a frequent record that there is a constitutional tendency in thyroid disease, the cases given in the table above show this rather strikingly. Each one of them taken alone probably defines a case of thyroid failure. No two of them are exactly alike in the general laboratory picture. The father was the first member of the family to be admitted to the clinic, his presenting difficulty being asthenia of comparatively brief duration. His history showed a susceptibility to infection which dated back to early childhood. He had always been constipated and had developed some minor paraesthesias. The physical findings were substantially normal. His basal rate as recorded was distinctly above the truth. The urea index was distinctly below the normal, and this coupled with his low phthalein output and the urine examination suggested a slight lowering of kidney permeability. Radiographic findings were normal, but a laryngological examination demonstrated infected tonsils. Other features of the examination can be seen in the table.

The oldest son was the tall, thin atypical "thyroid failure." Fatigability was his principal difficulty. He also had frontal headache, chronic catarrh, and an earlier acute sinusitis with some paraesthesias of the extremities. His remaining examination was not striking except for a history of jaundice some years before. The

TABLE XX

	Hyperthyroid			
	1	2	3	4
Case Number.	B-953	S-1895	S-1188	S-1596
Diagnosis.....	+	+	+	+
Sex.....	F	F	F	F
Age.....	(yrs.) 6	72	33	23
Height.....	(cm.) 115.5	161.0	162.0	161.0
Weight.....	(kgm.) 17.7	48.0	45.0	85.9
Weight Deviation.	(%) -13	-18	-29	+35
Lung Volume Deviation	(%) -56	-39	-35	-22
Basal Rate Deviation..	(%) +18(?)	+22	+44	+55
Blood Pressure..	(mm.) 120/55	170.82	122/50	136.58
Pulse Rate.....	(per min.) 116	100	92	122
Temperature.....	(deg. F.) 99.2	98.8	98.0	98.6
Alveolar CO <sub>2</sub> ...	(mm.) 38	41	44	44
Urine Volume.	(cc.) 170	960	960	1400
Spec. Grav....		1.026	1.014	1.023
Albumin....	+	+	0	+
Casts...	0	0	+	0.
Sugar.....	0	+	+	0
Total Nitrogen	(gms.) 2.03	3.74	8.91	6.60
Residual Nitrogen	(%) 7.7	7.2	12.8	8.3
"Urobilinogen"	0	0	0	0
Phen. Sulph. Phthal.	(%) 61	69	55	48
Galac. Tol. Deviation	(%) -50	-	-	-
Non-Protein Nitrogen	(mgm.) 30	32	29	26
Uric Acid.....	(mgm.) 3.3	3.0	2.7	2.6
Sugar.....	(mgm.) 93	105	109	75
Haemoglobin....	(%) 95	80	90	88
Erythrocytes....	(10 <sup>6</sup> ) 5.14	4.68	4.93	4.32
Leucocytes....	(10 <sup>3</sup> ) 6.75	5.05	7.90	9.50
Neutrophiles...	(%) 42	70	53	68
Lymphocytes.....	(%) 35	25	38	29
Eosinophiles.....	(%) 10	1	1	1
Monocytes.....	(%) 13	4	8	2
Misc.....	(%) 0	0	0	0

1. Young child, exoph. goiter. B. M. slight; sugar, large change.
2. Incipient recurrence long after operation.
3. Prompt recurrence after operation.
4. Recurrent after operation with obesity.



physical findings were substantially normal. X-ray studies showed obstruction of the nasal fossae.

The second child, a daughter, is also an atypical "thyroid failure." The history as given is not suggestive and the physical findings were equally normal.

The youngest member of the family is perhaps less certainly hypothyroid. He did show a slight thyroid enlargement, the only one of the group giving any evidence of goiter. We were unable to study this case as thoroughly as desired and are by no means certain of the diagnosis. The slight glycosuria is a disturbing note, although several causes not incompatible with a thyroid failure could produce it. That he is "endocrine" is obvious. Further study would be necessary to fix with certainty the focus at fault.

#### GROUP VII. HYPERTHYROID.

The following group of cases have been selected as presenting certain possible interesting points in connection with a definite hyperthyroidism. The enormous general literature dealing with the condition renders it unnecessary to discuss cases falling in any of the conventional groups.

#### PLATE V



Case B-953

CASE B-953. This little patient, a child of five, was referred to us with all of the outward evidences of well-marked exophthalmic goiter. The presenting complaint was her bulging eyes coupled with a marked nervousness. At about the age of a year and a half the mother noted that the child's eyes were beginning to bulge and that she was becoming nervous. The condition has been progressive, and because of her unusual appearance she has had difficulty with her schoolmates and had to be withdrawn shortly after entrance into her school. She had been under intermittent observation but without treatment.

*Family History:* The child is the oldest of three children, the other two being normal. The remaining history is not informative.

*Past History:* She was normally delivered, and breast fed for the first six months. She had measles at the age of four. The vision was not very good. She was subject to head colds and to sore-throats. She experienced no difficulty in breathing; the bowels were regular; there has been excessive perspiration on hands and feet and a skin eruption on the former.

*Physical Examination:* The patient was a well-developed but thin Italian child, 5 years of age, presenting a very marked exophthalmos, and moderate symmetrical thyroid enlargement. There were pulsations all along the anterior and lateral surfaces of the neck, and a well-developed bruit. The child showed lid lag and a positive Stellwag sign. The tonsils were large, cryptic and apparently infected. There was tachycardia and apparently some cardiac enlargement. The pulse pressure was very high. There was a slight fine tremor of the fingers, the knee jerks were equal and very active. The extensor test of the thigh suggested by Dr. Lahey was positive.

*Laboratory Summary:* The child was somewhat underweight and much below her predicted lung volume. A series of basal rate determinations gave a moderate increase above prediction. The standards for children of this age are not well defined and the value given represents a probable value from a series of different comparisons. There was tachycardia, a slightly febrile temperature, and a large pulse pressure, to which attention is again called. The urine was very scanty and contained albumin. The residual nitrogen fraction was normal. The sugar tolerance was half the normal level. The blood morphology showed a 10 per cent eosinophilia.

*Radiography:* There was no substernal enlargement; the heart was normal; the lungs showed mottling at both bases; the skull was normal; the optic canals were symmetrical and 4 mm. in diameter.

*Skin Examination:* This defined the eruption on the hands as punctate purpuric lesions of unknown etiology. In the examiner's opinion they were not associated with the exophthalmos.

*Surgical Examination:* "The thyroid was moderately enlarged. The exophthalmos was disproportionate to the apparent degree of toxemia."

*Chest Examination:* There was no evidence of present pulmonary disease. The cardiac enlargement was confirmed.

*Neurological Examination:* The findings were normal except for those characteristic of exophthalmic goiter.

*Nose and Throat Examination:* Cryptic tonsils of moderate size were found.

*Cardiogram:* This showed a normal mechanism with accelerated (125-135) rate. There was some evidence of possible auricular hyper-trophy.

*Eye Examination:* The discs were yellowish and there was a thin retinal pigment with the choroidal vessels visible. The sclerae were bluish. The fields could not be obtained owing to the age of the patient.

*Discussion:* That the patient presented goiter with exophthalmos was obvious. Apparently, however, the toxicity of the gland was low insofar as the basal rate would be taken as an index. On the other hand the sugar tolerance was much depressed, and while some depression would be anticipated with an overactive thyroid, the relative

degrees were disproportionate if the usual case be taken as a criterion. Suggestion of a congenital internal hydrocephalus was made by one of our associates, but x-ray examination of the skull gave no supporting evidence. As the child was not toxic to any marked degree she was discharged from the hospital without treatment with recommendation that she return within a few months for further study. In our experience primarily overactive thyroids at times undergo a spontaneous functional involution. Further, the extreme youth of the little patient seemed to warrant delay, since no evidence of marked toxicity was apparent. Two months later, however, the child having presented certain disturbing symptoms, she was referred to the Lahey Clinic for operation. We are much indebted to Dr. Robert L. Mason for the following information:

"She was brought to the Deaconess Hospital on May 17. With her history you are, of course, familiar. On examination she presented a rather marked exophthalmos. The thyroid was uniformly enlarged and had the firm elastic consistency of a hyperplastic gland. Her pulse rate was 132, weight was 40 1/2 pounds. The remainder of her general physical examination was essentially negative. Basal metabolism test the following morning showed a rate of +60. We believed the child to present a definite case of primary hyperthyroidism. She was placed on a pre-operative regime which included five minims of Lugol's solution three times a day, a high calorie diet, and rest in bed. On May 31st, her metabolism had dropped to +4; her pulse rate to 80 and she had gained 1 1/4 pounds. We thought her ready for operation."

"On June 1st, operation was done. Four fifths of a definite hyperplastic gland was resected. Pathological examination of the excised thyroid tissue showed it to be primary hyperplasia with moderate involution. There was a mild reaction following operation, which, however, had entirely subsided by seventy-two hours. Her subsequent course was satisfactory and uneventful. On discharge, she was doing very well. She was given a prescription of five drops of Lugol's solution taken each week for three months, at the end of which time she was to have a check up for metabolism."

In the case of this child we are by no means certain that the obvious thyroid condition was not complicated by some other and extraneous effect. The preliminary study gave several possible evidences that this might be the case. She will be studied later in the hope that additional light can be thrown on the condition. It is quoted here, partly because of the somewhat unusual youth of the little patient and because it possibly illustrates the sugar anomaly of which note was made in the earlier section. In this connection we have had opportunity to make a more complete study of an adult woman in whom no complicating superimposed effect could be demonstrated. The significant data are given in the following table:

TABLE XXa

Date	Interval (Week)	Blood Pressure	Pulse	Basal Rate	Weight	Sugar Tolerance
Dec. 6, 1926	0	132/54	84	+6	32.2	
Dec. 13, 1926	1	118/50	86	+11	32.1	
Dec. 27, 1926	2					-75%
Jan. 7, 1927	2	128/48	100	+16	49.6	
Jan. 15, 1927	1					
Jan. 22, 1927	1	126/42	78	+12	47.7	
Mar. 14, 1927	7	108/52	71	-15	51.4	
Mar. 28, 1927	2					+50%
April 25, 1927	4	116/58	73	-11	52.2	
June 6, 1927	6	112/58	80	+2	50.2	
to						
Dec. 1, 1927	24	110/60	88	+6	51.6	10 tests
Dec. 28, 1927	4					
Feb. 3, 1928	9	120/48	102	+17	49.0	-50%
to						
May 4, 1928	13	138/68	88	+11	49.3	
May 18, 1928	2	130/72	96	+35	48.8	
May 24, 1928	1					
July 7, 1928	2	116/68	52	-28	54.5	
July 14, 1928	1	118/70	64	-31	55.0	
July 16, 1928						=0

This patient was a young woman of 29, first seen on December 6, 1926. She presented a clear-cut outward appearance of exophthalmic goiter, was emaciated, intensely nervous, and showed all the conventional stigmata. She gave a history of good health except for a poor appetite up to the preceding July. At this time her appetite became voracious, and at the same time her friends called attention to the protrusion of the eyes. The condition progressed and in September her attention was called to the palpable thyroid enlargement. The family history that she gave was entirely irrelevant. In her own personal history, an attack of measles at the age of 4, and three or four minor infections during the preceding year, were the only points of comment. The menstrual history had been an entirely uneventful one up to a year previously. At this time the periods fell to two days and with a very scanty flow. The basal rate determination showed the normal value of +6 per cent, a pulse rate of 84, and a normal systolic and low diastolic blood pressure. As her basal rate was wholly incommensurate with her patent goiter condition, and the degree of toxicity which she exhibited, it was repeated and +11 per cent recorded. Her sugar tolerance was found to be notably low, at a level, in fact, which we had never before recorded in uncomplicated thyroid hyperactivity. Subsequently the patient became very toxic. A test on January 7 showed a basal rate of +16 per cent, progressive tachycardia and loss of weight. She was operated upon one week later, after the usual period of rest, and shortly dropped to a mild hypofunctional level. There was distinct clinical improvement and during the latter part of this period a sugar test was performed which showed a tolerance 50 per cent above prediction. For the next few months she kept in touch with the Clinic and at the end of about a year from her first contact began to give signs of a renewed toxicity, although the basal rate presented the normal value of +6 per cent. Her sugar tolerance at this time was —50 per cent. Operation was postponed, but in May of the current year it became patent that the condition was progressive with steadily increasing toxicity. A second operation was performed, and the tests since made showed a drop of the basal rate to a frank hypofunctional level, while the sugar tolerance has become normal, the patient has gained weight rapidly, the exophthalmos is greatly diminished, and the patient regards herself as entirely cured. The interesting feature in this case is the marked divergence of the sugar tolerance with the slight variations in the basal rate. This reverses completely the usual thyroid finding in which even marked over- or under-activity of the gland are accompanied by relatively slight changes in the sugar tolerance, and in approximately two-thirds of our cases by no departure from the normal. A possible explanation already touched upon could lie in the existence of a second hormone produced by the thyroid which under ordinary conditions is but slightly influenced by changes in glandular activity. In a few cases, however, this hormonal influence seems to be the one involved, that agent which controls the oxygen consumption being but slightly influenced. That the patient was toxic there can be no possible doubt. The recession of the symptoms with each of her operations, but more marked with the second, and the absence of any other disorder discernable after careful and thorough study, would seem to indicate a definite thyroid aberration as the cause of her difficulties. The suggestion offered above is no more than a suggestion. We have had, however, a few cases in the past (4 or 5) which have shown analogous aberrations of carbohydrate metabolism. In cases in which thyroid disease was definitely established and no superimposed effect could be demonstrated, the fact that, from the clinical side, individual patients will show their greatest response to thyroid

extract alone, to thyroxin alone, or to a judicious blending of the two, may well be pertinent to this thesis.

**CASE S-1895.** This case was reported as of possible interest as demonstrating a recurrent hypothyroid condition, after a considerable interval, in a woman of advanced years. The patient presented as her chief complaints bronchial asthma which had begun after her thyroid operation; arthritis in the back and left leg, from which she had suffered for the past four years; a general itching of the body similar to that experienced previous to the operation, and which was of but brief duration; tachycardia which had developed in the past few weeks.

*Family History:* The father died of diabetes, the mother of cancer. Many of the immediate family were above average height. No other case of thyroid disease was recorded.

*Past History:* The patient reported the minor childhood diseases, but none of the graver complaints of adult years. A thyroidec-tomy in 1921 was her sole operation. She had recently developed what she termed a "thyroid headache" similar to that experienced previous to her operation. There had been marked loss of hair at that earlier time, and again recently. The teeth had all been removed, and there was more or less soreness in the mouth, which latter was of recent date. She complained of dyspnoea and palpitation at the two intervals significant in relation to her thyroid. She had lost 15 lbs. in the past four months. Her menstrual history was uneventful. She was very fatigable. During her long married life she had one miscarriage and had borne one child, which subsequently died of epilepsy.

*Physical Examination* showed a fairly well-preserved but under-nourished woman of 72 whose hair was coarse and thin, no exophthalmos, teeth all gone and the buccal mucous membrane normal. There was no evidence of thyroid enlargement, there were minor abnormal sounds in the chest. Arteriosclerosis was present. There was some tachycardia and a few minor neurological findings which were not confirmed by the neurologist.

*Laboratory Summary:* The patient was 18 per cent underweight and significantly below her predicted lung volume. There was a hypertensive blood pressure, rapid pulse, urine showing both albumin and casts, and protein intake far below a maintenance level. The remaining findings were not strikingly significant.

*Radiography* of the chest showed scattered calcified nodes along the track of the large bronchi and emphysema. Both antra were obscured.

*Neurological Examination* noted the tremor of the hands, but gave no evidence of organic neurological lesion.

*Cardiogram* showed simple tachycardia with premature ventricular beats.

*Chest Examination* confirmed the harsh respiratory sounds over both bronchi, together with some peribronchial dullness.

*Laryngological Examination* gave entirely normal findings.

*Discussion:* The picture here is typical of a mild and, in this case, recurrent hyperthyroidism. Whether the infected antra played any part in this event must be a matter of speculation. X-ray

TABLE XXI

	Pseudo-Nephritis		1	2	3	4
Case Number....	B-110	B-110-a	B-560	S-1396	B-738	B-730
Diagnosis.....	—	—	—	—	— (surg.)	—
Sex.....	F	F	M	F	F	M
Age..... (yrs.)	53	53	11	24	52	26
Height..... (cm.)	157	157	131.0	152.0	176.3	190.5
Weight..... (kgm.)	69.5	59.0	29.1	69.0	85.0	81.9
Weight Deviation..... (%)	+26	+7	-10	+30	+7	*(+7)
Lung Volume Deviation..... (%)	-48	-14	-16	-12	-35	-26
Basal Rate Deviation..... (%)	-32	+35	-52	-39	(-16)	-40
Blood Pressure..... (mm.)	124/80	116/68	102/60	90/74	150/84	120/68
Pulse..... (per min.)	72	78	76	51	64	60
Temperature..... (deg. F.)	98.2	98.2	97.0	97.2	97.8	97.4
Alveolar CO <sub>2</sub> ..... (mm.)	37	(33)	41	36	45	50
Urine Volume..... (cc.)	750	580	1700	1310	1230	620
Spec. Grav.....	1.016	1.018	1.010	1.012	1.019	1.031
Albumin.....	0	0	+	0	+	0
Casts.....	0	0	+	0	0	0
..... (gms.)	4.22	5.90	7.85	5.17	10.33	8.33
..... (%)	6.5	5.0	12.9	9.5	8.5	12.4
.....	0	0	0	0	0	+
Phen. Sulph. Phthal. . . (%)	32	55	21	32	39	48
Galac. Tol. Deviation . . (%)	±0	±0	+33	not done	±0	±0
Non-Protein Nitrogen (mgm.)	36	26	33	32	35	31
Uric Acid. (mgm.)	1.9	3.2	2.5	3.2	3.8	3.3
Sugar. (mgm.)	87	77	87	85	93	100
Haemoglobin (%)	90	95	100	85	85	90
Erythrocytes (10 <sup>6</sup> )	4.83	4.72	5.50	4.20	3.78	4.76
Leucocytes (10 <sup>3</sup> )	5.25	6.05	11.70	7.30	3.50	5.70
Neutrophiles. . . (%)	48	51	26	49	17	56
Lymphocytes... (%)	49	40	71	40	14	32
Eosinophiles. . . (%)	0	1	0	2	3	2
Monocytes.... (%)	3	8	3	9	6	9
(Basophiles). . . (%)	0	0	0	0	0	1

\*See discussion of case.

1. Presenting so-called "Epstein's Nephrosis."

2. Characteristics cardiac findings

3. Complicated with primary anaemia.

4. Complicated with earlier hyperpituitarism spontaneously arrested.

\* Sitting Height Index < 0.50.

#### GROUP VIII. "PSEUDO NEPHRITIS"

**CASES B-110 AND 110-a.** The patient's chief complaint as presented was a bloating of the face, which gradually extended over the chest and arms. This at first began some two months before admission, but probably had been going on for some time prior to this. She had been getting progressively fatigable and nervous, felt that her aural acuity was diminishing, and that there was a general failure of all of her powers.

*Family History* was not informative.

*Past History:* The patient reported all of the minor ailments of childhood and pneumonia at 36 complicated by a secondary anaemia. The deafness really began some 16 years previously, but it had been disquieting only for the last few months. She had been gaining weight recently and suffered from dyspnoea. She had always been constipated; the appetite had been poor. The marital history showed two children and two miscarriages. The catamenial history was normal, including a slow and uneventful menopause, which apparently was completed a few months before her admission.

*Physical Examination:* The patient was a well nourished, somewhat obese woman of 53. She presented some loss of hearing. The

skin was dry, glossy, and hypertrophic; the eyelids swollen, palpebral fissures narrow; practically all teeth had been removed, those remaining being abscessed; the thyroid was not enlarged; the heart action was slightly irregular, and there was a slight systolic murmur. The remaining findings were substantially normal.

*Laboratory Summary:* The patient was 26 per cent overweight and had lost nearly half of her predicted lung volume. The basal rate was —32 per cent. The urine volume was scanty, elimination poor. The phthalein output was distinctly below the normal. Protein intake, as shown by the urinary nitrogen, was far below a maintenance level. The blood analysis gave evidence of lowered kidney permeability. The blood showed a marked relative lymphocytosis.

*Neurological Examination* showed certain paræsthesias, an 8th nerve disturbance, and a possible loss of deep sensation in the right leg.

*Eye Examination* showed a definite contraction of form and color fields, most pronounced in the upper quadrant, the latter due to lid droop.

*X-ray Examination:* The sella was normal; the heart showed right-sided enlargement.

*Pelvic Examination:* Findings were normal except for minor residua of child-bearing.

*Discussion:* The possible suggestion of primary anæmia had been ruled out by observations made elsewhere. The picture here presented was consistent with a hypothyroidism with myxedema. The patient was placed on thyroid extract, and two months later returned for a brief series of check observations. Clinically she was greatly improved. The skin had cleared entirely; she had lost 10.5 kgm. weight; the lung volume was slightly better; the phthalein output had risen to a normal level; her nitrogen elimination had improved; while the blood nitrogen values had diminished to levels consistent with her protein intake. While the blood was still lymphoid in type, the degree had diminished, and the general formula far more nearly approached the normal.

#### GROUP IX. THYROID FAILURE WITH MISCELLANEOUS COMPLICATIONS

CASE B-560. The patient was a boy of 11 whose case had been diagnosed as one of Epstein's nephrosis. Two series of studies were available which had been made at earlier periods. The boy was first admitted to the hospital in January, 1919, then being 4 years of age. He was kept under observation for nearly a year, and was discharged as having chronic parenchymatous nephritis. During this period he had shown marked ascites of the abdomen and, on a number of occasions, quantities of fluid of the order of a quart had been removed by tapping. The urine had shown a characteristic picture. He remained in good health until July, 1921, when he was readmitted in a markedly edematous condition. There had been vomiting for twenty-four hours. The condition progressed, and early in August a decapsulation operation was performed on the right kidney, and in September on the left. There was rapid improvement and he was discharged in November. Three years after a tonsil and adenoid operation was performed, and in March, 1925, he was again readmitted with marked edema. The condition cleared up in a few days, however, and he was discharged with a confirmation of the earlier diagnosis. He was admitted to this

service in June, 1926, with marked anasarca and ascites. Again the condition gradually cleared up and in July, 1926, further study was undertaken.

*Family History:* A general history of renal disease was obtained.

*Past History:* Beyond the facts already discussed, the patient reported scarlet fever, influenza, several minor ailments, tonsillitis, and bronchitis.

*Physical Examination* showed a somewhat undersized boy of 11, with face somewhat full and puffy, general nutrition fair; the nose was broad and flattened, the nares not obstructed. He showed a minor cervical adenopathy, but no thyroid enlargement. The heart showed oft systolic murmur at the apex, which was not transmitted. The lungs and abdomen substantially normal. The remaining findings were not significant.

*Laboratory Summary:* At the time of this examination the acute phase had passed. The urine volumes were ample, albumin and casts were both present; elimination was good; the residual nitrogen was high; the phthalein output at this time distinctly low. The boy was 10 per cent underweight and had shown a basal rate of —52 per cent. This very low level would be influenced, naturally, by any residual trapping of fluid, but as the lad was 10 per cent underweight and gave no positive evidence of the presence of fluid, the value observed was felt to be approximately correct. The blood pressure was low, the temperature slightly sub-normal. The sugar tolerance at this time was slightly above the normal. The blood constituents were normal and gave no evidence of retention. There was a slight leucocytosis, with very marked increase in the lymphocytic fraction.

*X-ray Examination:* The skull, sinuses, and kidneys were normal. The sella was normal, except for some evidence of bridging between the clinoids.

*Eye Examination:* Fine granular pigmentations throughout the retinae ("pseudo-snuff fundi"), which is probably normal. There was a slight blind spot enlargement and a possible slight contraction of the color fields, which could not be confirmed, however, a few days later.

Studies of the urine showed no loss of concentrating power in the kidney, there being a variation of ten points. The general picture was one of renal irritation without functional damage.

Cholesterol and fibrinogen of the blood were high; plasma protein, low.

*Discussion:* With just recognition of the kidney condition, the remaining picture was essentially that of a thyroid failure. Part of the earlier work on this patient had been done elsewhere, and we have reason to believe that some thyroid extract had been exhibited, but no chronological record was available. On May 28, a basal determination was carried out which showed a low blood pressure, a rapid pulse, and a rate recorded as —15 per cent. As the patient was nervous, however, this could be discounted materially. On June 10, with subsiding pulse rate, the basal rate was about —50 per cent. On June 23, the pulse was above 100 and the basal rate +18 per cent. Three days later the pulse was 88 and the basal rate +11 per cent. On July 6, the pulse was 72, temperature and blood pressure definitely low, and a basal rate of —26 per cent was obtained. As will be seen in the table, the basal rate again went still lower, and then, on thyroid medication, there was a prompt return to the normal level. The



patient was discharged shortly after in a greatly improved condition. We have not been able to effect a later contact, but from the fact that there have been no further hospital entries recorded it seems fair to assume that there have been no serious recurrences.

In Epstein's original papers, he lays great stress on the blood cholesterol and fibrinogen. So far as we are informed, no adequate studies have been made on the influence of thyroid failure on these substances. While this is not the place to carry out a discussion, the writers are entirely unconvinced as to the existence of the so-called Epstein nephrosis as a disease entity. Certainly in the present case there is a typical picture of thyroid failure, which is supported by the patient's very prompt response to thyroid medication. This case opens up a number of lines of study, some of which are at the present being prosecuted. Whether there be a definite relationship between kidney and thyroid function, or whether the former be influenced by the metabolic disturbance incident to hypofunction of the latter, is a question that awaits future resolution. The case is offered here only as it presents certain points of general interest.

**CASE S-1396.** This patient is included in the group not because she presented a complication of thyroid disease, but because of a very interesting series of cardiograms produced by her condition and subsequent medication.

The chief complaint was of nervousness and fatigability. Four years prior to admission her husband had died after one year of married life. This produced a profound emotional shock, followed by loss of weight and general nervous imbalance. One year subsequently she began to increase in weight, and this had progressed to a point of definite obesity. During the past year she had had numbness and pricking sensations in the hands and had become relatively insensitive to hot objects.

*Family History:* Not significant.

*Past History:* Beyond minor ailments of childhood, the patient's life had been medically uneventful. She did not become pregnant during her brief marital experience. She complained of some dyspnoea, constipation, and some indigestion with flatulency. She had become decidedly asocial since the onset of the present illness. The menstrual history showed a normal onset, but with marked irregularity, the periods occurring from two to three months. The periods themselves were somewhat profuse.

*Physical Examination:* The patient was a well-developed, obese young woman of 24, presenting the typical facies of myxedema. The hair on the vertex was dark and very scanty, the skin very tough, thick, dry and scaly; palpebral fissures greatly narrowed, eyelids puffy. There was pain on pressure over the right maxillary sinus. The blood pressure was low and there was a marked bradycardia (44). A few scattered rales were reported in the right chest. There was some tenderness in both lower quadrants. The remaining findings were not significant.

*Laboratory Summary:* The patient was much overweight. The basal rate was —39 per cent, with very low blood pressure, bradycardia and subnormal temperature. The urine was substantially normal except for poor elimination and high residual nitrogen. Her protein intake was inadequate. The blood showed a definite lymphocytosis.

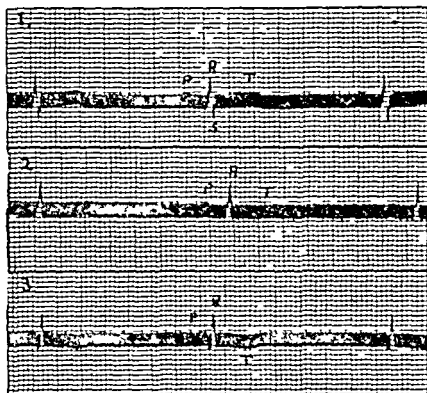
*X-ray Examination:* Chest, heart and lungs were normal. The teeth showed one unerupted molar and one periapical abscess. The skull was normal.

*Pelvic Examination:* The findings were normal. The tenderness in the lower quadrants was not confirmed.

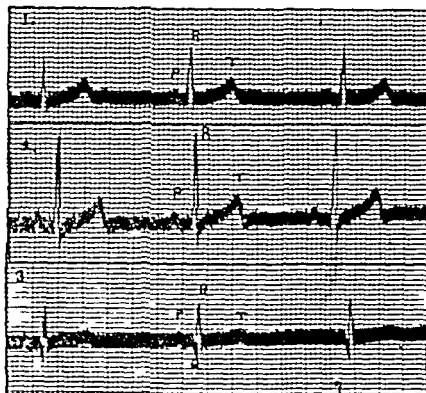
*Cardiogram:* The graph apparently showed a normal mechanism at a retarded rate (see plate).

### PLATE VI

Case S-1396. Cardiograms before and after treatment.



March 1, 1927



April 27, 1927

*Audiogram:* Normal conditions were found.

*Laryngological Examination:* Tonsils were suspected, but infection could not be demonstrated.

*Neurological Examination:* Conditions were normal except for findings associated with the myxedema.

*Eye Examination:* The form and color fields very markedly contracted symmetrically; the blind spots, much enlarged.

TABLE XXI-a

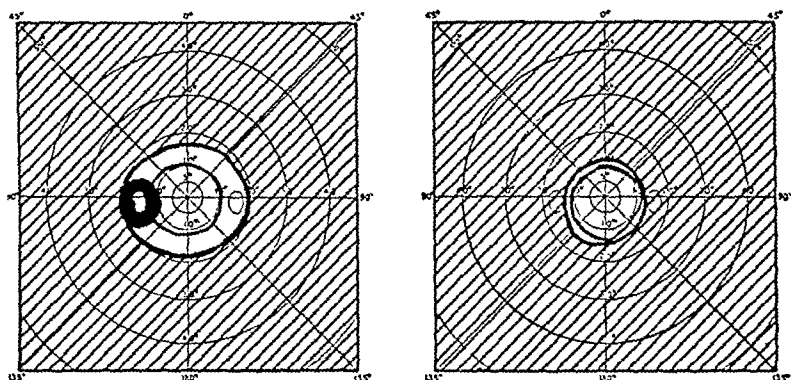
CONTINUOUS RECORD OF CASE OF HYPOTHYROIDISM

Date	Basal Metabolism	Blood Pressure	Pulse	Weight
March 1.....	-39%	90/74	51	69.0
15.....	Began medication			
April 2.....	-11%	102/66	50	62.3
9.....	-10%	96/50	48	60.5
	Lowered dose			
18.....	-19%	90/38	46	58.5
	Increased dose			
23.....	-11%	86/38	44	58.4
30.....	-10%	94/42	52	57.3
May 16.....	-4%	98/54	54	57.5
21.....	-3%	98/54	58	57.5

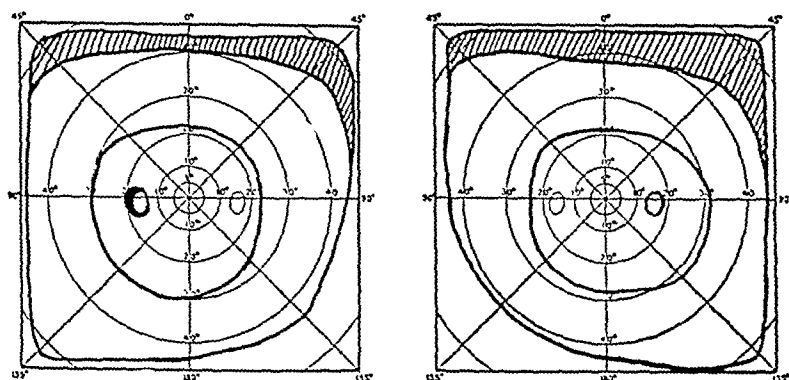
*Discussion:* The patient presented a typical picture of hypothyroidism with myxedema. She was placed on thyroid medication and in a few weeks obtained a normal basal rate, with the loss of slightly more than 10 kgm (see table). Clinically, she showed the remarkable improvement which may be confidently anticipated in simple cases of thyroid failure. The cardiogram became entirely normal (see plate). An interesting feature was the persistence of the low blood pressure and bradycardia after all of the other findings had become normal. A second eye examination was made and the earlier much contracted fields found to have been entirely corrected except for a slight upper field cutting, due to lid droop (see plate).

## PLATE VII

Case S-1396. Eye plots before and after treatment.



March 5, 1927



September 28, 1927

CASE B-738. The patient's chief complaint was of asthenia, which first became remarkable 2 years ago. It had been progressive, and during the preceding four months had become seriously crippling. A diagnosis of thyroid failure had been made, but no thyroid medica-

tion had been given. About four months ago she began to experience numbness and stinging in the extremities, and this had spread somewhat to involve the entire limb. For five years past she has had more or less trouble with eczema. Recently the blood calcium was found to be deficient and iron injections were given.

*Family History* was not significant.

*Past History:* The patient had minor ailments in childhood, and in 1907 a partial thyroidectomy. In 1918 the uterus was removed and an appendectomy was done. For the last 2 years there had been almost constant headache. The hair had grown gray and become very dry during the same interval. The eyes were easily fatigable. During the last year she had developed a rash in the mouth, and at times small ulcers with white centers had appeared on the tongue. There was occasional dyspnoea, a tendency to constipation and flatulency. The patient was unmarried; the menstrual history was substantially negative except for scanty periods and termination with the fibroid operation above referred to. Recently she had experienced coldness of the extremities and some edema.

*Physical Examination:* The patient was a well-developed and well-nourished woman of 52, somewhat above the average height. She exhibited a moderate exophthalmos and a vesicular eruption on the tongue. The skin was dry and hypertrophic throughout, with eczematous patches on the extremities; brown macular eruptions were observed on both legs. There was a slight, coarse tremor of the hands and the reflexes were sluggish.

*Laboratory Summary:* The patient was 7 per cent overweight. The basal rate as recorded was —16 per cent, but this was probably somewhat above the truth. The blood pressure was slightly high. The urine showed albumin, and the residual nitrogen an upward tendency. The sugar tolerance was normal. The blood analysis gave no evidence of retention. The blood morphology showed an anæmia of the primary type with a leukopenia.

*Skin Examination* defined a papulo-vesicular eczema and suggested that the pigment areas were due to Schamberg's disease.

*Neurological Examination* demonstrated loss of bone conduction in the lower extremities and noted the paræsthesias already recorded.

*X-ray findings* of the skull and sella were normal.

*Eye Examination:* The fundi showed a slight amount of vascular sclerosis; there was cutting of the upper form fields, due to lid droop.

*Neutral Red Test:* Dye was not recovered in two hours.

*Gastric Analysis:* No free hydrochloric acid was found.

*Diagnosis:* The patient presented a post-operative hypothyroidism complicated by a primary anæmia. The latter was shown to be in a state of remission, with characteristic regeneration, as evidenced by repeated typical blood examinations.

CASE B-730. This case presents several points of interest, as a current endocrinopathy is complicated by residua of an earlier and different endocrine disease.

The patient's chief complaint as given was of pain in the back, from which he had suffered for three or four weeks, and which followed a period of hard manual labor. As a matter of fact, the patient was sent in for the evaluation of certain physical abnormalities, coupled with a definite mental arrest.

*Family History:* Irrelevant.

*Past History:* The patient reported minor ailments, smallpox at 21 (there having been an unsuccessful vaccination at the age of 18), several traumatic injuries not germane to the present study. He had had severe frontal headaches for the past year. All of his teeth were removed at the age of 22 because of severe caries. Prior to this, there was almost daily toothache. Up to the age of 16 he was of normal size. He then began to grow rapidly and in a relatively short time reached his present height of 190.5 cm., which is probably greater, as the patient's posture is poor and he exhibits a definite stoop. He complained of an occasional fleeting pain lasting only a minute or two in the upper right quadrant.

*Physical Examination:* The patient was a noticeably tall, somewhat spare young man, 26 years of age. There was some enlargement of the frontal bossæ and a definite protrusion of the lower jaw. The teeth, as noted above, were all missing. The tonsils were enlarged, and there was a slight thyroid enlargement. In addition, a slight inguinal and cervical adenopathy was noted. The testicles were somewhat atrophic, the skin dry, the posture, as noted above, was poor. Mentally, the patient was slow and immature and definitely below an average intelligence. He further presented a speech difficulty, articulation being thick and obscure.

*Laboratory Summary:* By the Dreyer standard, the patient was 7 per cent overweight, but as the sitting height index is slightly less than 0.50, he was actually slightly underweight. There was some loss of predicted lung volume. The basal rate was —40 per cent, with a tendency to lowered blood pressure and bradycardia less clearly shown in the present than in other records. The temperature was slightly subnormal. There was oliguria, a high residual nitrogen, and a somewhat low phthalein output. The sugar tolerance was normal; blood constituents normal; a blood morphology, substantially normal.

*Cardiogram:* This shows a normal mechanism with simple bradycardia (pulse rate 51).

*X-ray Examination:* The skull, sinuses, and sella were normal.

*Audiogram:* Slight general loss of hearing in both ears was noted.

*Eye Examination:* The discs were yellow, the blind spots greatly enlarged, and both form and color fields notably contracted symmetrically.

*Duodenal Function (McClure):* The values were all low, indicating a definitely disturbed liver function.

*Icteric Index* was high.

*Van den Bergh:* A strongly positive reaction was obtained.

*Discussion:* This is a case in which the findings are susceptible of several possible interpretations. Its resolution must rest on the basis of probability. The patient's outward habitus is, of course, suggestive of a pituitary overactivity. That such a condition obtained, we believe there can be no question, and, equally, that there was a spontaneous arrest some years before we saw the patient, which left the gland at a present normal level. While it is true that the pituitary could be in a functional transition from an initial hyper- to a terminal hypo-active state, there is nothing in the present study to support such a theory. The level of the basal rate, the bradycardia, the

oliguria, coupled with the absence of a high blood uric acid and an eosinophilia, are all observations against a pituitary diagnosis. True, there is a positive urobilinogen test, but the demonstrated dysfunction of the liver offers a direct cause for its appearance. It should be further noted here that we do not always find changed sugar tolerance with liver dysfunction. That this should be so is to be expected, in view of the large number of wholly divergent causes which produce a picture significant of disturbed liver function. The storage and metabolism of sugar by the liver is but one of its many functions. That some of these may be profoundly disturbed without producing correlative changes in all, is too patent to require discussion. The patient's atrophic testicles play no part in the picture. We have shown that ablation of the testicles in adult years will not affect significantly any of the objective findings of the complete laboratory analysis. The diagnosis on this patient is a current thyroid failure coupled with some measure of liver dysfunction. The physical habitus of the patient reflects an earlier endocrinopathy involving the pituitary which has ceased to be actively operative.

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# THE RESULTS OF REPLACEMENT THERAPY IN AN HYPOPHYSECTOMIZED PUPPY: FOUR MONTHS OF TREATMENT WITH DAILY PITUITARY HETEROTRANSPLANTS\*

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Recent experimental studies on rats, cats and dogs have shown conclusively that the hypophysis is not essential to life in these animals, and although its removal is accompanied by remarkable physical changes resulting primarily from retarded development, and that although their span of life after hypophysectomy may be shorter than that of the control, it is of sufficient length to indicate that the removal of the pituitary has not resulted in death.

Aschner (1) in 1912 published striking photographs of hypophysectomized puppies of various ages which had remained infantile in appearance and size until sacrificed. Using the buccal approach, his hypophysectomies were performed as early as the eighth week of life and the animals lived for months.

The intracranial approach devised by Dandy and Reichert (2) has made possible a successful and complete hypophysectomy in puppies as early as the third week of life. This procedure is facilitated by the preoperative intravenous injection of a hypertonic solution of sodium chloride to shrink the brain.

Evans and Long (3) have found that fresh anterior lobe fluid will produce gigantism if given intraperitoneally to immature rats. This extract was found to stimulate hypophysectomized rats to normal growth but failed to affect their sex glands.

Putnam, Teel and Benedict (4) have just reported the use of an anterior lobe extract in a young bull dog over a period of eight months with progressive gain in weight above that of its littermate control. They also state that in preliminary ex-

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periments a restoration of growth was brought about in hypophysectomized dogs and rats.

The negative results of transplantation experiments in dogs may be attributed to the inappreciable effect of the absorption of a single transplant.

Smith (5), using daily transplants of the fresh pituitary gland of rats, was able completely or in large measure to overcome the disabilities caused by hypophysectomy in immature rats. This replacement therapy led to a restoration of the normal rate of growth, induced the normal function and corresponding histological appearance in the sex organs and led to a reparative phenomena in the atrophied thyroid and suprarenal cortex. Smith and Engle (6) were able to induce pre-



Fig. 1. Littermate females, 6 weeks old and just before hypophysectomy on 16. 16, wt. 2.76 kgm.—17, wt. 2.5 kgm.

cocious sexual maturity both in immature and in hypophysectomized rats, in two animals within thirty-six hours, by their fresh daily transplants.

The illuminating results obtained by Smith and Engle (7) with daily hypophyseal homeo- and hetero-transplants in mice and rats suggested an investigation of the effect of daily injec-



tions of fresh rabbit pituitary gland in an hypophysectomized puppy.

Replacement therapy was begun in a female puppy which had had a total hypophysectomy when six weeks old. At the time of operation the base of the brain in the infundibular region was cauterized by heat to insure complete removal of hypophyseal tissue. This animal was constantly kept with her



Fig. 2. Two months after total hypophysectomy 16, wt 4.0 kgm 17, wt 5.1 kgm

littermate control, also female, living out of doors and in the sunshine. Figure 1 shows their appearance just before operation on dog 16. The subsequent photographs and x-rays, Figures 2, 3, 4 and 5, substantiate the fact that after months of observation she remained infantile, failed to grow, retained the puppy face and hair, failed to erupt permanent teeth and ex-

and tibia remained open in both dog 16 and in the control dog 17. Measurement of the tibia during this period showed an increase of 0.7 cm. in length in dog 16, while the tibia of dog 17 increased 1.9 cm. Injection treatment was instituted at the age of seven and one-half months when the distal epiphysis of the femur in dog 16 was nearly ossified, and open epiphyseal lines remained at the proximal end of the femur and both ends of the tibia. At this time all four epiphyses were practically ossified in the control dog 17, which had now attained full growth (Figure 5).



Fig. 5. X-ray plate of femur and tibia when 7.5 months old and 6 months after hypophysectomy.

For the first two months of injection therapy the tibia of dog 16 increased 1.0 cm., whereas in the control there was no increase in length, a further indication that maturity had been reached in the control when replacement therapy was begun. Measurement of the femur during this same period showed a

growth of 1.0 cm. in dog 16 (Figure 9) and practically no change (0.1 cm.) in dog 17. At the end of this period the distal epiphysis of the femur in dog 16 was completely ossified, with the proximal epiphysis of the femur and distal epiphysis of the tibia nearly closed. At this time, however, all the epiphyses of the tibia and femur were found to be completely ossified in dog 17. Measurement of the skull taken frominion to



Fig. 6. Three days after replacement therapy started on 16, with daily injections of fresh rabbit's whole hypophysis. External genitalia swollen within 48 hours after first injection.

tip of maxilla showed an increase in length for the initial two months of 0.7 cm. in dog 16 (Figure 8), while in dog 17 there was only 0.2 cm. of growth.

At the end of the third month of therapy both epiphyses of the femur in dog 16 were closed and those of the tibia were nearly ossified. At the end of the fourth month the distal

epiphysis of the tibia was closed and the proximal one nearly ossified. Thus during the first two months of replacement therapy the changes in the epiphyseal lines indicated that the puppy was approaching maturity and that this had been attained during the last two months.



Fig. 7. After two months of replacement therapy, when 9.5 months old and 8 months after hypophysectomy. Operated animal fully as active and alert as control. 16, wt. 4.5 kgm.—17, wt. 9.8 kgm.

There was no increase in length of the skull in dog 16 and an increase of only 0.2 cm. in length of each femur and tibia during the last two months of injection treatment.

At the end of four months of replacement therapy in dog 16 the skull had lengthened 0.7 cm., the femur 1.2 cm., the tibia

1.2 cm., while in dog 17, during the same period, the skull had lengthened only 0.2 cm., the femur 0.2 cm., and the tibia 0.3 cm.

The weight of the experimental puppy increased at a little below the normal rate for the first three weeks after hypophy-

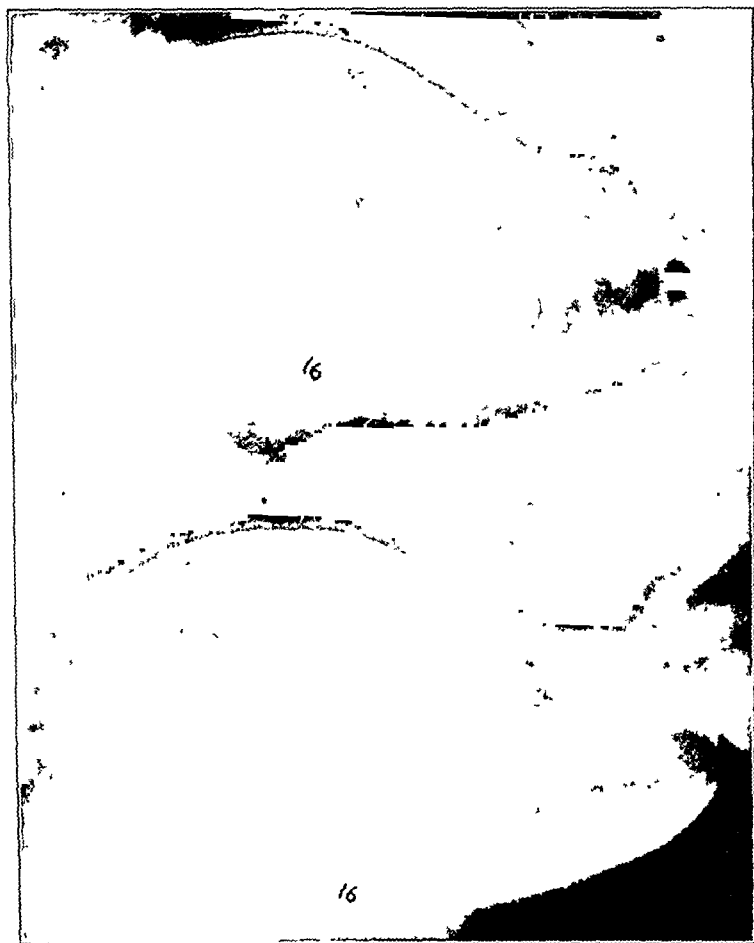


Fig 8 X-ray plate of head of hypophysectomized puppy just before (upper) and 2 months after (lower) replacement therapy to show growth of skull and eruption of permanent teeth.

sectomy, then showed no appreciable gain for a subsequent period of five months. During the four months of replacement therapy a slight increase in weight occurred, as shown by the chart (Figure 12). Adipose tissue, especially in the groin, defi-

from the hypophysectomized puppy and the control for the purpose of comparative histological study. The adrenal of the control was 4 mm. longer and 1.5 to 2 mm. greater in diameter than that of dog 16. On microscopic examination the gland from both animals had a normal cytological appearance with approximately the same relative proportion of the three layers of cortex to the medulla.



Fig. 11. Swelling of external genitalia of dog 16 persisted throughout four months of replacement therapy.

Microscopic sections of the thyroid of dog 16 showed a parenchymatous hyperplasia with cells of the cuboidal type which formed to a depth of two or three layers in many places. In some areas the acini were nearly filled with these cells. The interstitial cells were more abundant than those of the control

and there was an increase in the number and size of the blood vessels throughout the stroma. The colloid appeared normal. In the thyroid of the control the acini were lined with a single layer of cuboidal epithelium. There was no evidence of hyperplasia and the colloid appeared normal.

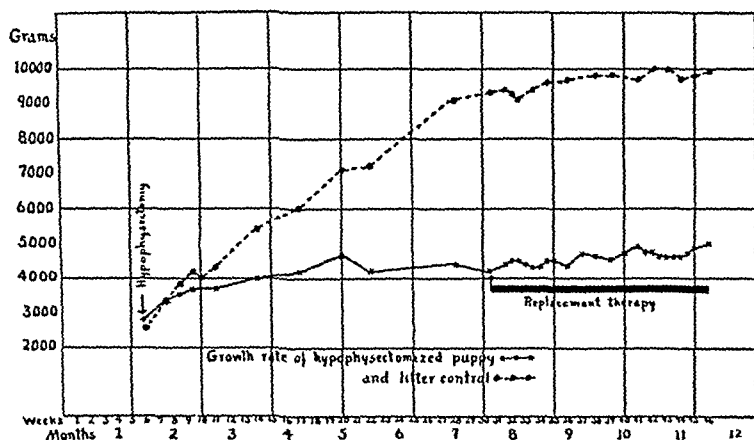


Fig. 12. Chart of the weight of the dogs 16 and 17.

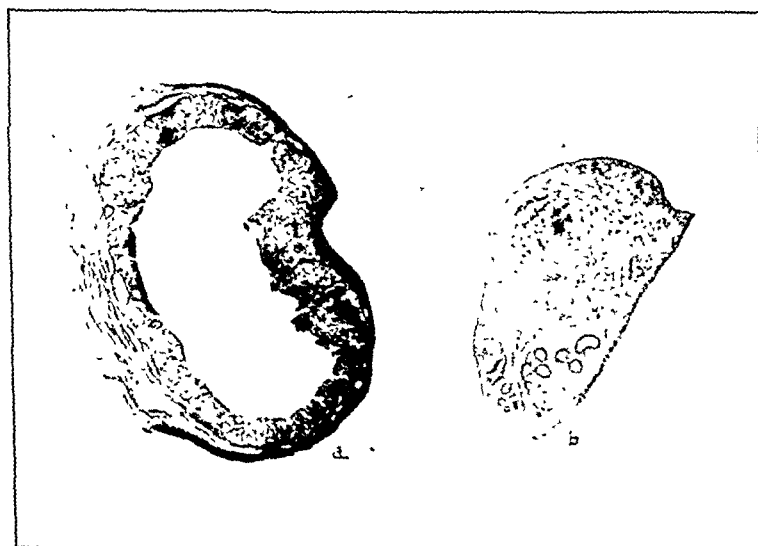


Fig. 13. a. Ovary from hypophysectomized animal four months after replacement therapy, showing cystic corpus luteum. b. Ovary from control animal. Magnification about 4x.

The ovary of the hypophysectomized animal was larger than that of the control and the cornua of the uterus were pink with numerous enlarged and tortuous vessels on the surface. The microscopic sections of the ovary and uterus were studied and described by Dr. C. F. Fluhmann. The ovarian sections of dog 17 were normal, there being numerous primordial follicles in the cortex and several developing Graafian follicles deeper in the substance of the ovary (Figure 13b). There was no evidence of corpus luteum formation.

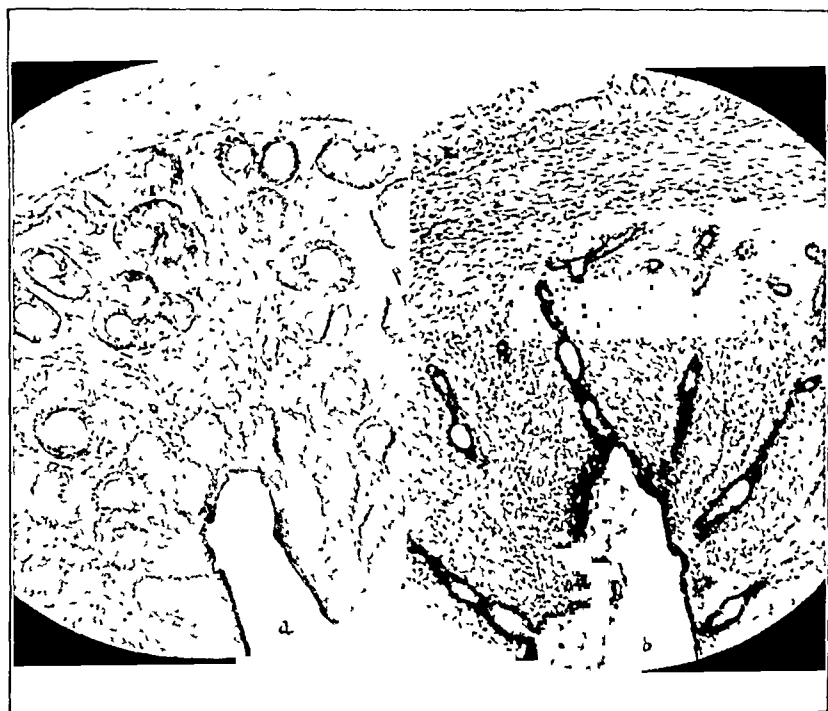


Fig 14 a Endometrium from hypophysectomized animal four months after replacement therapy, showing stage of gland hyperplasia b Endometrium from control animal showing resting phase Magnification about 100x

Grossly the ovary taken from dog 16 was almost filled by a cystic structure measuring 1.5x1.0 cm. (Figure 13a). The wall was of a grayish white color, with a festooned border and the cyst contained a thick mucoid material. Microscopically the cortex showed normal ovarian tissue with several primordial follicles and one early Graafian follicle. The cyst was lined by a fairly thick convoluted layer of well preserved lutein cells



The tissue was extremely vascularized but there was no evidence whatever of hemorrhage. The inner lining of the cyst was a thin layer of newly formed granulation tissue.

The cross section of the uterine horn of dog 17 measured 4.25 mm. The endometrium varied from 1.0 to 1.25 mm. in thickness and presented the appearance of the resting phase (Figure 14b). There were comparatively few glands. These were straight and were lined by a low type of cuboidal epithelium which showed no evidence of secretory activity. The stroma was cellular and there were but few blood vessels, although there was an extensive infiltration of free blood attributed by Dr. Reichert to trauma during the operative removal.

The section of the uterine horn of the treated puppy also measured 4.25 mm. in diameter. The endometrium was somewhat thicker than in the control animal and its general appearance conformed to that phase of the cycle referred to by Keller (8) as the stage of gland hyperplasia (the pseudopregnant period of Marshall and Halnan) (Figure 14a). The most striking feature was the tremendous increase in number, size and tortuosity of the glands throughout the whole depth of the endometrium. The individual cells both of the gland and the surface epithelium were of a high cylindrical type and showed evidence of intense secretory activity. The stroma was markedly oedematous and there was a considerable increase in the number of blood vessels but no free extravasation of blood. The myometrium presented no abnormalities.

#### SUMMARY

The disabilities arising from hypophysectomy in a six weeks old female puppy were in a large measure overcome by four months of replacement therapy with daily fresh heterotransplants of rabbit pituitary.

The puppy remained in a state of oestrus throughout the four months of replacement therapy, although the control never came into heat.

Failure to obtain marked increase in growth and weight in this experimental animal can be attributed to the fact that replacement therapy was instituted at the stage of life when the control had attained full growth.

Experiments are now in progress in which replacement treatment was started soon after total hypophysectomy when the control as well as the experimental animal were still immature.

I want to acknowledge the devoted care and attention given these animals by Ludwig Rübzig and John Kratsch, and to express my appreciation of the excellent photographic work of W. J. Taylor.

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# THE ROUTE OF ABSORPTION OF THE ACTIVE PRINCIPLES OF THE POSTERIOR HYPOPHYSIAL LOBE

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## INTRODUCTION

In 1910 Cushing and Goetsch (12) showed that human hydrocephalic cerebrospinal fluid, when concentrated twenty-fold on a waterbath and injected intravenously into an anaesthetized rabbit or dog, gave pressor and other responses not dissimilar to those of aqueous extracts of the fresh posterior hypophyseal lobe. They therefore postulated on a physiological basis

a route of absorption for the principle which had earlier been advanced by Herring (25) on histological grounds, i.e., the principle elaborated by the pars intermedia passes into, and is possibly activated by, the posterior lobe, whence it streams as particulate hyaline matter up through the infundibular stalk into the cerebrospinal fluid of the third ventricle, and is thence absorbed by the blood stream into the body; this may be designated an indirect or transneural route. The validity of the specific physiological responses upon which this postulation was based was questioned by Carlson and Martin (9), and subsequently Jacobson (28) showed that analogous concentrates of artificial spinal fluids made up solely of inorganic salts could duplicate the cardiovascular and diuretic effects obtained by Cushing and Goetsch. Later, however, with the advent of the oxytocic method, numerous investigators (10, 46, 36, 29, 35) reported the presence of an ecboic substance in the cisternal and ventricular (but not spinal) fluid of all mammalia investigated.\*

In 1922 Maurer and Lewis (34), on the other hand, postulated a purely vascular route of absorption for the active principle, largely on negative and philosophic grounds. Histologically, a vascular route for presumably evident *anterior* lobe secretion (19, 39) is as firmly supported as is the transneural route for *posterior* lobe secretion. Hogben (26) in the meantime demonstrated (in 1923) that posterior lobe secretion is blood-borne in amphibia, and Krogh (32), with the advent of his anuran melanophore preparation, that presumptive pituitrin is present in greater concentration in equine serum than in equine cerebrospinal fluid. However, he arrived at an apparent impasse to the extension of the method in the allergic reactions of anuran vascular systems to foreign sera. This difficulty, as well as the allergic response of the oxytocic preparation to serum proteins, has been overcome in the present work by utilizing Smith and McCloskey's (43) observation that pituitrin dialyses readily.

Partition of presumptive pituitrin from serum proteins, and biotitration of the active substance in resulting dialysates, has been the basic method used in the investigation reported below.

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\*The problem was attacked by Dr. S. C. Harvey in this laboratory in 1915, but the technique of the oxytocic method had not then been dependably standardized and his results were not published.

Normal human, bovine, and canine blood (and cerebrospinal fluid) has been utilized, as well as that of dogs with experimental lesions, and of those showing spontaneous pathological deviations from normal. Identity of the active substance in the dialysates has been conjectured through changes after hypophysectomy, and the probable route of absorption indicated by changes after physiological isolation of the supra-infundibular cerebral ventricle. For titration both the melanophore preparation (37) and the oxytocic method have largely been used.

#### METHODS

Only final methods used are given; preliminary work and failures are occasionally indicated in Results.

**DIALYSING MEMBRANES (22):** About 20 cc. of a 6 per cent solution of dry Mallinckrodt pyroxylin in a 15 to 85 (by weight) mixture of absolute ethyl alcohol and Mallinckrodt anaesthetic ether (4 per cent water and alcohol content) was poured into a heavy dry 30 cc. test tube. The tube was then inverted and allowed to drain for 30 to 45 seconds into the stock bottle, while being rotated with its mouth just immersed in the ether vapor filling the bottle above the solution. A strong draft of air was then drawn deeply into the tip of the inverted, slanted, and rotated tube for 60 seconds; this was conveniently accom-

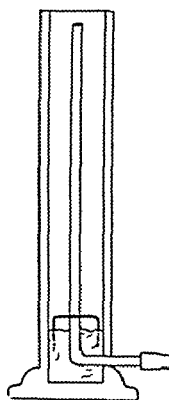


Fig. 1. Convenient air suction tower for making dialysing membranes without blemishes; semi diagrammatic cross-section. A wooden casing (container for Esbach albuminometer tube may be used) incloses a glass tube embedded in a plaster of paris base. Two wires are so embedded that the test tube mold cannot touch the plaster, insuring good airway.

plished by the device shown in Fig. 1, without spoiling the membrane. The tube was quickly and gently filled to the brim with water for 2 minutes; inverted; the top of the tube reamed with the edge of a forceps to free the membrane at its lips, and the membrane withdrawn by gentle traction. It was occasionally necessary to introduce a

few mils of water between the membrane and the tube to facilitate separation. The membrane was filled with distilled water and immersed in a large jar of distilled water, where it remained for 16 to 24 hours before use.

Opaque white spots on these membranes are microscopically sieves, caused by too thick a layer of collodion; and their presence below the neck of the membrane obviously makes the dialysing sac unfit for use. If the tube used as a mold has blemishes on its inner surface, tiny pin-like holes are pulled in the membrane as it separates. The tube mold finally found satisfactory should be marked legibly and used for nothing else. The permeability of the membranes decreases: (1) with increase in the ether percentage; (2) with duration of air drying; and (3), to some slight extent, with the strength of the collodion. Collodion membrane molds of 250 mil and 500 mil Erlenmeyer flasks are made similarly.

**DIALYSIS:** The fresh clotted blood samples were centrifuged 20 minutes at 1000 r.p.m. The serum was pipetted off into empty dialysing sacs, where the volume obtained was measured by displacement. The sack was then immersed in a dialysing chamber containing two volumes of fresh mammalian Ringer-Locke solution; with the cylindrical graduates used herein, this sufficed to bring the Ringer-Locke to the level of the serum. The labelled chamber was placed in a refrigerator for eight hours. The rare presence of small amounts either of erythrocytes or of laked blood in the serum does not particularly matter, though the presence of much of the latter seems at times to be the concomitant of detectable histamin contamination. Sacs were removed, and the solution warmed and gently agitated just prior to oxytocic titration. If for any reason dialysis was continued longer than 24 hours, Ringer-Locke solution lacking glucose and bicarbonate was utilized. Cerebrospinal fluid, because of its low protein content, was not dialysed before testing.

**OXYTOMIC TITRATION (7, 44, 48): Apparatus:** A 25 cc. hard glass chamber, immersed in a large water bath maintained at 37.5° C., was arranged to fill (or to empty) at will with warmed Ringer-Locke solution oxygenated through a glass tube having a pore of exit opposite a glass prong on which was impaled the isthmial end of half of a guinea pig bicornuate uterus (Fig. 2). A second similarly accoutred chamber was used in the same bath, so that the other half of the uterus could be utilized constantly to check results of the first. The chambers were encircled with rubber bands to mark the 15 cc., 20 cc., and 25 cc. levels. With the 25 cc. chambers necessary to avoid undue dilution of "unknowns," the unwieldy, expensive, and elaborate tanks used in standardizing pituitrin become unnecessary; casual knowledge of laboratory glass blowing will enable one to assemble for a few cents the simple apparatus depicted. Oxygen was bubbled through a 2 per cent aqueous solution of sodium bicarbonate before delivery into the titration chamber, in accord with the suggestion of Smith and McCloskey.

**Guinea Pigs:** Virgin guinea pigs, raised segregated from males, when about 225 to 250 grams in weight, yielded satisfactory uteri. Even so, those in rut, with swollen pink vulvae or turgid injected uteri were rejected, for these were hyperirritable and gave preparations of such spontaneous fluctuations in tonus as to make interpretation of results difficult or impossible.

**Solutions:** This modification of mammalian Ringer-Locke (pH 8.3) was used: NaCl 9.0 gm; KCl 0.42 gm.; CaCl<sub>2</sub> 0.24 gm; MgCl<sub>2</sub>

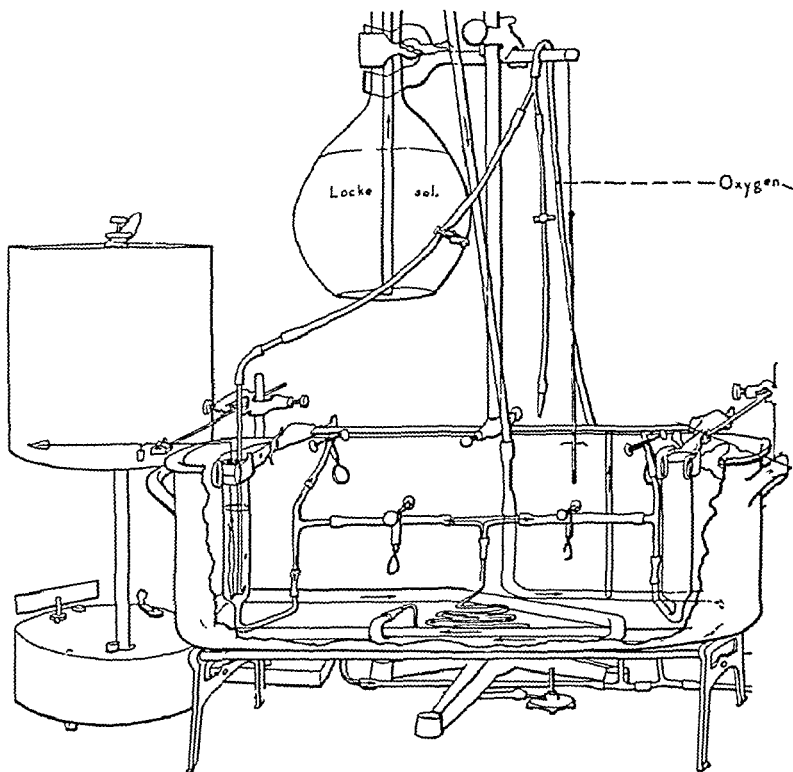


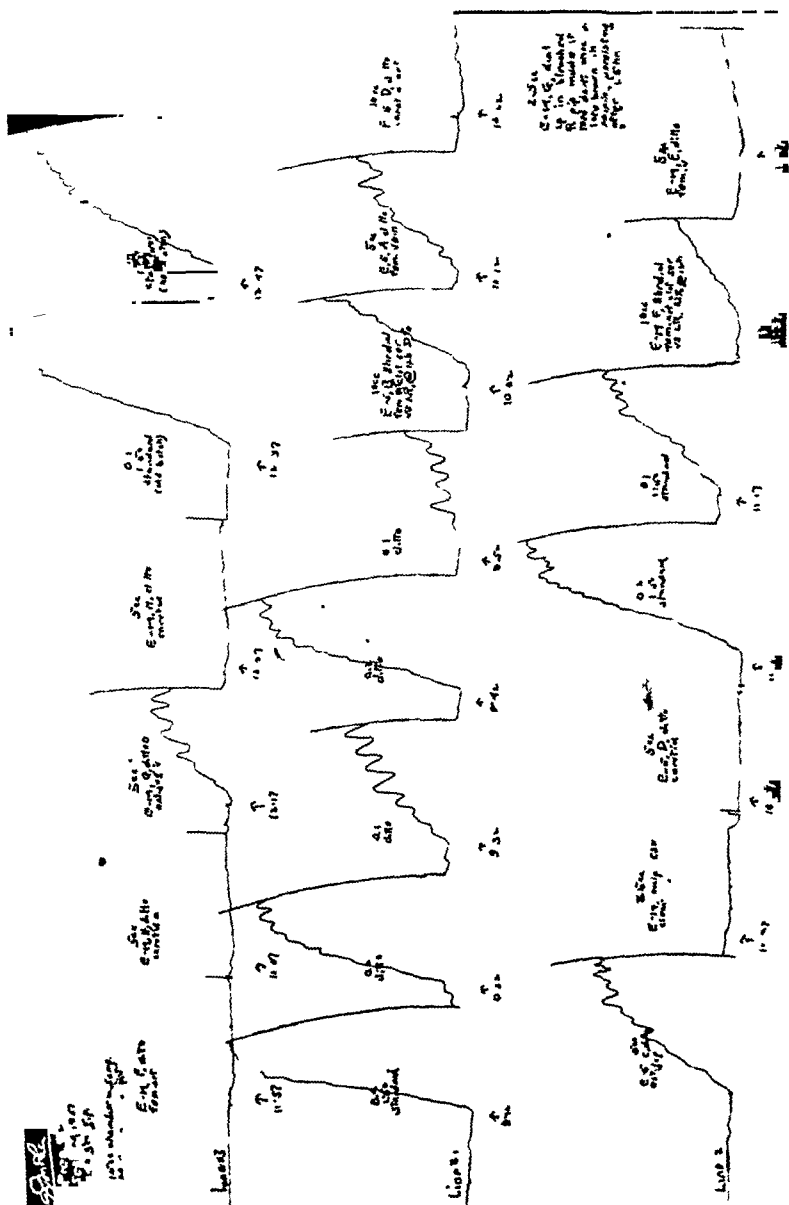
Fig. 2 Simple and satisfactory oxytocic titration apparatus. A large fish kettle filled with tap water is raised on a stand and heated by a micro Bunsen burner, a thermometer is suspended in the bath. The 25 cc. hard glass titration chamber, at either end of the bath are made of filter tubes. These are fed with Ringer-Locke solution by gravity through the large bore glass warming coils at the bottom of the tank, a smaller bore coil may be added as a hydrostatic brake, if desired; access of the fluid to the titrating chamber is controlled by a pinch cock. A second pinch cock is on a tube leading over the back of the tank to a main hose end, dependent over the table edge, forms a second or evacuating siphon. It is convenient to include as a tap on the main a siphon for emptying the large tank itself, as shown. The rod supporting the oxytocic preparation in the titration chamber is hollow. Its lower end is drawn out into two prongs opposite one another; one having a slight downward angulation is used to impale the isthmial end of a guinea pig uterus (this prong *must* be of glass); the other is filed off to allow a small orifice for escape of oxygen. The opening in the rubber stopper should be as large as possible, to allow introduction of samples by pipettes. The oxygen is bubbled through a 2 per cent aqueous solution of sodium bicarbonate in a Wolfe bottle (not shown—behind tank) before delivery to the titration chamber. For illustration, the left hand titration chamber only is connected as for use.

0.005 gm.;  $\text{NaHCO}_3$  0.5 gm.; dextrose 0.5 gm.; distilled water 1000 cc.; the first five were made up in 20-fold concentration, the bicarbonate being added in solution last, with constant stirring. It was filtered through paper after two hours. The dextrose was added to each fresh dilution from stock. The pituitrin standard was a 0.1 per cent extract of Smith and McCloskey's (42) infundibular powder in 0.25 per cent acetic acid; the powder was brought to a rapid one minute boil in a sterile beaker, filtered sterilely, sealed sterilely in 2 cc. hard glass ampoules, and stored in a refrigerator until used. The powder used was obtained commercially from the Lederle Laboratories, but was checked by oxytocic methods in this laboratory against a standard sample obtained from and through the courtesy of the U. S. Hygienic Laboratory. The histamin was a 0.1 per cent aqueous solution of Burroughs & Wellcome ergamine acid phosphate, made and sealed with sterile precautions in 2 cc. hard glass ampoules, and stored in a refrigerator. Fresh dilutions of standards were made for each titration, with Luer syringes and serological pipettes.

*Procedure:* The large bath was filled with water at  $38^\circ\text{C}$ ., and the micro-Bunsen burner lighted; temperature equilibrium at  $37.5^\circ\text{C}$ . to  $0.1^\circ$  or  $0.15^\circ$  was obtained in about an hour. A guinea pig was weighed, killed by a blow back of the occiput, stretched on a dissecting board, its ventral coat moistened with water, and the abdomen opened. The uterus was identified, one horn picked up at its junction with the salpynx, the broad ligament cut with scissors close to the uterus, the isthmus split down to just above the cervix, and the lateral half removed. Without shifting the forceps at the uterosalpyngial junction, a pin hook was passed through this extremity (muscle lever thread being already tied in place on the hook), the muscle laid on a thin pad of gauze, its isthmial end impaled on the glass prong of the titration chamber unit, transferred at once to fresh, warm Ringer-Locke solution in the chamber, and attached to the muscle lever, where a 1 gram counterweight was placed 1.5 cm. from the fulcrum. The specimen was thus placed in the chamber with a minimum of handling and trauma. The remaining half of the uterus was quickly mounted in the other chamber, both being in place within 3 to 4 minutes of the death of the guinea pig. A slow stream of oxygen was admitted to the chamber. Thirty minutes was allowed to overcome the initial irritability of the uterus.

It was then washed, and 1000 to 2000  $\mu\text{m gm}$ . (0.1-0.2 mil of 1:50 dilution) pituitrin was introduced into the 20 cc. chamber. The uterus reached its full contraction in 3 minutes; the kymograph was then stopped, the uterus washed, and 7 minutes allowed for relaxation. Several contractions with known amounts of pituitrin in varying quantities were recorded in each chamber, while a graduate of unknown was allowed to warm in the large bath. Five or 10 mils of an unknown were now introduced with a warmed pipette into a 15 cc chamber (the 20 cc. chamber. just large enough to immerse the preparation completely. was drained of 5 cc. the instant before the unknown was added), and a 3-minute contraction curve recorded; the uterus was again washed. and had relaxed for the next titration in 7 minutes. The time intervals adopted were always followed consistently throughout a titration. After 5 or 6 unknowns were titrated, the uterus was restandardized with known pituitrin. and further unknowns assayed; the series always ended with a restandardization. With this method. and these solutions (pH 8.3), the response of the uterus became erratic if ever. in the 5th or 6th hour of titration; when this happened it was discarded.





*Interpretation:* The uterus of a virgin guinea pig responds with identical contractions to identical successive doses of pituitrin (15, 16): within certain limits, it also responds quantitatively to varied doses (44). The bulk of use of the oxytocic preparation has been for biological assay and standardization of posterior lobe extracts, where slightly submaximal contractions are used and striven for; this type of curve is well known in the literature. Very small doses of commercial pituitary extracts (Parke-Davis; Armour), or of standard pituitary powder extract, or of weakly acid extracts of fresh posterior lobe (see Discussion), however, produced changes in tonus which are not so familiar (46), which are not so exquisitely quantitative, and whose variations are more labile when standard conditions are not strictly observed. The sensitivity of a good preparation varies slowly throughout a titration, until after a lapse of hours it may eventuate in a spontaneous irritability such as to make the uterus unfit for use. In assigning a recorded numerical value to the height of a contraction produced by an unknown substance, not only must the rise be interpolated with good judgment between successive standardizations of the uterus, but results obtained from each of the two preparations be considered. One-half of a titration record is shown in Fig. 3. Initial response to introduction of a dialysate after pituitrin, or of pituitrin after dialysates, may be exaggerated. To aid in interpretation therefore it is well to introduce Unknown A first to Preparation 1, followed in sequence by Unknown B, etc.; while Unknown B should be introduced first to Preparation 2, and followed by Unknown A, C, etc.; and it is always well to give two or more doses of pituitrin in restandardization. The qualitative variations in the series of unknowns is furthermore checked by the simultaneously run melanophore biotitration mentioned below.

*Calculation:* Example: (Fig. 3, line 1, 10:12 p. m.) Thirteen mils of Dog E-5's serum from a clot of femoral vein blood was dialysed for 8 hours against 26 cc. of Ringer-Locke solution, resulting therefore in a 33 per cent dispersion of the dialysable substances at equilibrium. An osmotic rise of the serum in the sac does not interfere with concentrations, since dispersion of dialysable substances is uniform at equilibrium, and only initial volumes need be considered. Five mils of this dialysate, when added to 15 cc. of liquid bathing the uterus, produced 4/5 as high a contraction as the 9:32 and 11:17 titrations (the 9:52 contraction is ignored on the basis of the antecedent three contractions). Since each of these latter was a response to pituitrin in 100  $\mu$ mgm./mil concentration (0.1 cc. of 1:50 dilution of a 0.1 per cent extract of the powder, in a 20 mil titration chamber), the value of the 10:12 curve is 80  $\mu$ mgm. However, the 33 per cent sample was further diluted to quarter that strength through introduction into the Ringer-Locke of the chamber. and the ultimate dilution is one-twelfth (33 per cent  $\times \frac{1}{4}$ ), and the curve represents five-twelfths (5 cc.) of the initial serum's strength, or 180  $\mu$ mgm.

MELANOPHORE TITRATION (37): Krogh's frog perfusion preparation has been used as companion to the oxytocic method. to confirm qualitative variations in series of unknowns. In preliminary work it did yeoman service in detecting gross contamination with histamin far below the delicacy of chemical color tests [1000  $\mu$ mgm. (31)].

OPERATIONS: *Samples:* Bloods for titration were collected by aseptic exposure of the vessels under local anaesthesia (1 per cent novocain infiltration: no adrenalin). for eight months of the work; the procedure was quiet, the animals unexcited and docile throughout.

In the experiments of the first six weeks, however, the animal was anaesthetized with intravenous chloralose; external and internal jugular veins, carotid artery, femoral vein and artery, and endothelial wall of torcular Herophili, were exposed; the following day these now painless wounds were reopened aseptically and blood collected, also without excitement. This, however, was abandoned as containing more departures from normal than did quiet collection under novocain. Canine cerebrospinal fluid was uniformly obtained by cisternal puncture through the occipito-atlantoid ligament, the head being in moderate anterior flexion.

*Hypophysectomy:* A few hypophysectomies were done by the classical temporal route (11), but the majority by a transbuccal procedure described elsewhere (38).

*Sequestration of cerebrospinal fluid from the third ventricle:* To block the normal route of flow, the aqueduct of Sylvius was occluded by depositing accurately in it a gelatine shell inclosing iodized cotton (18) by a low . . . just above the occipito-atlantoid ligament. To a . . . ependymal and intraventricular venous absorption, the vena magna Galeni was occluded by two silver clips (13) just posterior to the two vena parvae Galeni (18). In one dog a bilateral lateral choroid plexectomy in addition was done (18), in an endeavor to avoid possibility of retrograde absorption through the plexus itself (23).

**NECROPSIES:** The brains of the two dogs with "sequestered" third ventricles were fixed preliminarily by injection of formalin into the carotids, and the entire decapitated head fixed for two weeks in formalin before the brain was removed and sliced into 5 mm. coronal sections. The hypothalamic regions of hypophysectomized dogs were removed en bloc with contiguous leptomeninges and dura, without disturbing relations. These were fixed in Zenker's fluid and completely sectioned serially at ten microns from chiasm to corpora mammalaria, and each section examined microscopically after staining with haematoxylin and eosin.

**UNITS (37):** Both Krogh units and metric  $\mu\text{mgm.}$  (micromilligram) are used in reporting results. Krogh (32) has previously used as an experimental unit 0.5 mgm. of international pituitary powder in a cubic meter of water. The reporting of such accurate, but infinitesimal, amounts involves either bewildering arrays of ciphers or cumbersome powers. The convenient metric micromilligram ( $1 \times 10^{-9}$ ) is therefore used herein in reporting results in terms of international pituitary power.

## RESULTS

**NORMAL DOGS: General:** Dialysing sacs made of parchment allowed passage of presumptive pituitrin at much slower rate than those of collodion made as described above. Even after 48 hours of dialysis equilibrium had not been reached. Six per cent collodion membranes in 50-50 alcohol-ether were too permeable, and after 36-54 hours allowed leaked haemoglobin when present to pass through. Double-dipped 4 per cent collodion 50-50 alcohol-ether membranes were satisfactory, but uselessly

hard to make. The 6 per cent 15-85 alcohol-ether membranes were uniformly adequate; after 8 hours in the dialysing chamber, serum and dialysate turned the skin of a frog perfusion preparation to same shades of color; longer dialysation did not detectibly increase the percentage of active substance in the dialysate. The use of small test tube brushes as whips for defibrinating blood, caused gross contamination with histamin; German silver wire whips were found satisfactory. In other early instances, contamination with histamin seemed to parallel roughly the degree of laking; the presence of histamin was deemed indicated by an abnormally high oxytocic titre in the face of blanching of the melanophore preparation.

*Distribution:* Bloods of thirteen normal dogs showed constantly presumptive pituitrin in concentration ranging from 75 to 360  $\mu$ gm. per mil, as measured by the oxytocic method. Five of these studied in detail showed concentrations in different vascular channels similar to those of Blood No. 8 from an exuberant male Airdale weighing 20 kgm.: external jugular vein 180  $\mu$ gm.; carotid artery 120  $\mu$ gm.; cisternal cerebrospinal fluid 120  $\mu$ gm.; femoral vein 70  $\mu$ gm.; toreular Herophili 360  $\mu$ gm. Three of these animals, however, showed smaller concentrations in the toreular (62, 75, 90  $\mu$ gm.) than in the external jugular vein (180, 120, 200  $\mu$ gm.). Blood in the small internal jugular of the dog had the same titre as the external jugular; the femoral artery carried more than the vein. That is, either toreular or jugular led, next in sequence was arterial blood and cerebrospinal fluid, and finally the lowest titres were obtained in the femoral vein. These qualitative differences were confirmed on the frog perfusion preparation.

*Transport:* Defibrinated blood serum was found to have slightly less presumptive pituitrin (120, 225, 150  $\mu$ gm.) than blood clot serum (140, 270, 165  $\mu$ gm.). The amount found in the erythrocyte residue after centrifugation of defibrinated blood was found to vary from 30  $\mu$ gm. to nothing, depending on the thoroughness of separation from serum. The amount found per unit of defibrinated whole blood was less than in defibrinated blood serum, probably due to inclusion of corpuscular volume in the whole blood. The amount found in the dialysate of whole blood allowed to clot in the dialysing sac,

either with collodion membranes (8 to 24 hour dialysis) or parchment (24 to 48 hours), was always small, probably due to mechanical interference with diffusion currents. These differences were confirmed qualitatively on the frog perfusion preparation. The detectible substance is therefore carried in the plasma, and greatest yield is obtained when the contracting clot is allowed or helped to express its own serum

**PATHOLOGICAL BLOODS:** One dog which developed a furious cryptepid infection of the dorsal snout 36 hours after a chloralose transtemporal operation was found at the 74th hour to be wholly without detectible presumptive pituitrin in blood or cerebrospinal fluid, either by frog or uterus method. A dog in extremis from meningitis was also found to be without detectible pituitrin.

A female Collie jumped as torcular blood was being collected; the needle passed through the sinus to the ventral bony plate of the skull; and although the dog appeared normal afterward, the bloods collected were found inactive on guinea pig uterus, and turned frogs' skin a peculiar shade of green not elsewhere encountered.

Successive samples taken from the external jugular during exsanguination have shown minor depressions of oxytocic activity, but the interpretation of this is obscure, inasmuch as the then increasing coagulability of the blood might indicate an epinephrin inundation. Epinephrin inhibits guinea pig uterine tonus. Whatever the cause, it was not sufficient to interfere perceptibly with qualitative relations in the frog perfusion preparation.

In a single instance, blood of an exsanguinated dog was found to be wholly inactive on guinea pig uterus, after standing as a dialysate (pH 8.3) for 54 hours, although this same dialysate was active on a frog perfusion preparation and showed enough unmistakable variation to allow interpretation of distribution of the active principle between corpuscles, sera, and whole blood; the possible significance of this is touched on below

A dog which had lost about 33 per cent of its weight while being "starved" for five weeks by only occasional gavage with glucose, with daily doses of morphia, was found to have a low normal concentration presumptive pituitrin and a normal distri-

bution<sup>1</sup>, while one which had lost about 50 per cent of its weight had a low concentration and an almost uniform distribution<sup>1</sup>. Both dogs fourteen days after resumption of feeding and discontinuance of morphia showed astoundingly high titres<sup>2</sup>, but after each gaining 25 per cent in weight in the following two weeks returned to normal concentration and distribution<sup>3</sup>.

OPERATIVE EXPERIMENTS: *Third ventricle sequestration*: An 18 kgm. female Collie and a 21 kgm. male Airdale each had a silver clip ligation of the vena magna Galeni 4 to 5 mm. anterior to the splenium; titration ten days later showed normal concentration and distribution of presumptive pituitrin. The iter was then occluded in both. Seven to ten days later they became irritable, relaxed, negativistic, idiotic in behavior, showed evident impairment of vision and had over 1.5 diopters elevation of the optic discs, deep pressure on abdomen or jugulars produced no acceleration in rate of flow from cisternal puncture needle. One (male) now showed no substantial alteration in the distribution formula<sup>1</sup>, while the other showed not only an elevation of the entire level of the curve, but also a reversal of the customary femoral artery-femoral vein ratio so frequently found later<sup>2</sup>; both, however, showed higher concentrations in the external jugular than in cisternal cerebrospinal fluid, and no lowering of presumptive pituitrin after ten days of "sequestration" of the third ventricle. The male was necropsied six days later, after another titration with similar findings; the clip was found tightly closed, and the iter plugged; the ventricles were somewhat dilated. A titration done on the female three weeks after occlusion of the iter showed

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Concentration of active substance in  $\mu$ mgm. per mil of serum in:

	External Jugular Vein	Carotid Artery	Femoral Artery	Femoral Vein	Cerebro- spinal Fluid
1.	115	38	118	150	90
	72	72	72	72	5
2.	1950	1400	1900	1300	240
	1500	700	1500	1160	120
3.	185	25	25	62	20
	150	100	100	125	10
4.	112	35	35	18	75
5.	840	740	520	720	720
6.	192	192	120	168	100 cis 100 lat
7.	18	18	18	150	8
8.	130	70	90	150	60
	375	75	375	600	16
9.	88	88	88	88	60
	5	5	54	54	144 yellow

that the active substance had fallen to normal levels, and that cerebrospinal fluids from the cisterna and from the lateral ventricle were of equal concentration, although less in amount than external jugular<sup>6</sup>. Necropsy three hours later (intra-carotid formalin) showed clip and plug in place, dilated iter anterior to plug, moderately dilated third and lateral ventricles, and a flattened Lima-bean shaped pituitary body.

*Hypophysectomy:* Six female dogs showed, within normal variation, the usual distribution of active substance. Most were given only a single preliminary titration, but one was titrated four times over a period of a month before operation. Four dogs showed the femoral artery-femoral vein inversion discussed below. They all received a transbuccal hypophysectomy, and had a transient mild polyuria for one to three days.<sup>\*</sup> Two to four weeks later some showed nearly complete absence of active principle<sup>7</sup>, while others showed either normal amounts or an intensification<sup>8</sup>. These latter, however, during the following month also dropped low<sup>9</sup> by the time others had astonishingly returned to normal. The two that had returned to normal were necropsied, along with one which had totally failed to show a drop. The remaining two developed bad dispositions, moderate obesity, sedateness, frowsy, bushy coats of very slowly growing fine hair, and their subsequent surgical wounds healed with considerable sluggishness; control animals kept under identical conditions did not show such changes. Within three to five months after operation, however, while the somatic changes remained unchanged, the oxytocic titre of their bloods and cerebrospinal fluid slowly returned to normal concentration and distribution. In every titration throughout their entire series, concentration of the active substance in the cerebrospinal fluid was less than in the external jugular vein, and the femoral artery-femoral vein inversion persisted. They were necropsied on the 88th and 152d day.

The 6000 serial sections of the hypothalamic regions of these five dogs were illuminating. The 152-day dog showed bilaterally, one to two mm. from the midline in the post chiasmal

<sup>\*</sup>The tuber cinereum of one was deliberately injured by a shallow incision 1 mm. long after an uncomplicated hypophysectomy. The animal had marked polyuria (5.6 liters daily), became comatose after 18 hours, developed a typical "cachexia hypophysopriva," and died with a rectal temperature of 94° F. at 40 hours.

and pre-infundibular region, a few 60-80 $\mu$  nests of pars tuberalis cells, which, as one progressed caudad, spread thinly over the inferior surface of the third ventricle as lateral epaulettes as far as the carotid artery, meeting, however, in the midline at the infundibular region, and covering thickly there a flat 0.1x1.0 mm. evagination of the floor of the third ventricle made up solely of neuroglial tissue indistinguishable cytologically from the walls of the ventricle itself (Fig. 4); this nubbin showed no infundibular cleft. After it had disappeared the carpeting of the pars tuberalis continued widely caudad for several millimeters. The 88-day dog was not dissimilar. The two dogs that had had an earlier and less prolonged dip from normal,

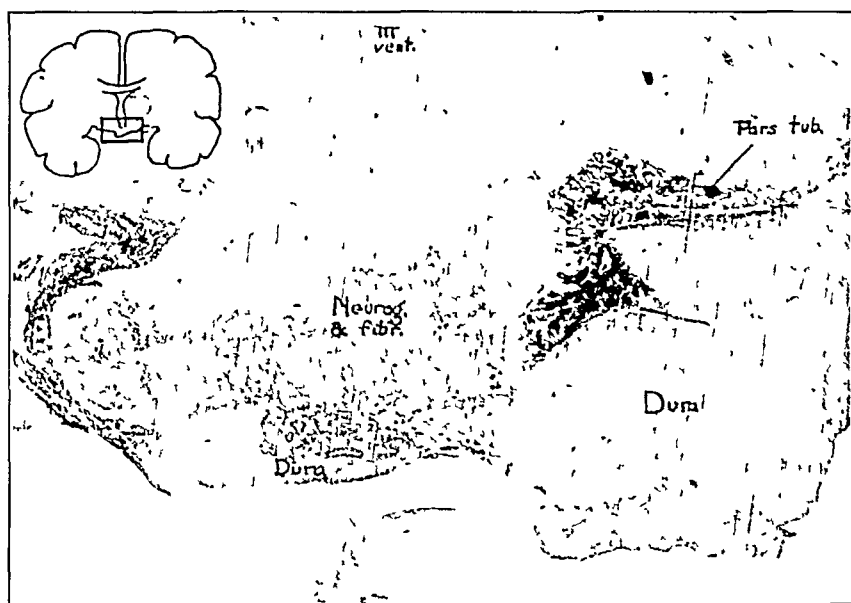


Fig 4 Photomicrograph of coronal section of Dog E-7's hypothalamic region in neighborhood of scar from removal of anterior and posterior lobes, together with as much hypophysial stalk tissue as possible. Note the neuroglial and fibroblastic reaction above the regenerating dura, and also the still existing lateral epaulettes of pars tuberalis. Other sections show still larger amounts of pars tuberalis. The neuroglial tissue immediately underlying the tuberalis cells on the left may be remnant of hypophysial stalk, even though no evidence of hypophysial cleft is found in other sections. The rectangle in the small sketch in the upper left hand corner shows the area enlarged in the photograph.

each showed the same picture, except that rather more (0.2x0.2 x1.1 mm) of undestroyed posterior lobe (or neuroglial repair) was present; one nubbin showed a definite short infundibular cleft. The dog which had shown no change in titre whatever



was without trace of pars anterior or pars intermedia, had the usual carpeting of the third ventricle by pars tuberalis, and a 1.0x1.0x0.8 mm. piece of stalk left, containing an infundibular cleft surmounted within the third ventricle by a small plug of neuroglial tissue. In this one dog, moreover, was there the sole suggestion of a few wisps of posterior lobe tissue, badly sclerosed and infiltrated, near the posterior adherent vascular attachment of the lobe to the brim of the sella turcica, from whence at operation it is removed with difficulty by curette.

*Tissue extracts:* Approximately 12 per cent extracts in  $\frac{1}{4}$  per cent acetic acid were made of thalamus, globus pallidus, and tuber cinereum, from five normal dogs. One set of these in 2 cc. ampoules was tried on an oxytocic preparation and all found to be inactive. When the subsequent four sets had been accumulated, however, and combined, the thalamus and pallidus were still found inactive, while the 8.5 cc. of tuber cinereum extract (neutralized to pH 7.4) produced a strong contraction calculated as representing 1100  $\mu$ gm. of pituitary powder per gram of substance. A roughly 1 per cent similar extract of canine pars neuralis four hours post-mortem produced curves interpreted as 28 mgm. per gram of substance. That is, posterior lobe contains at least 25,000 times as much active substance per gram as normal tuber cinereum.

*Ergothioneine* (21, 45): Just as other known organic dialysable substances of normal blood are inactive, so it was found that newly-discovered ergothioneine was inactive on guinea pig uterus in its physiological concentration (60 mgm./100 cc.) as well as twice this; while on the frog it was inactive both in physiological and ten-fold concentration.

*Human and bovine blood:* Were found to contain presumptive pituitrin, when dialysates were tested qualitatively either by the oxytocic or frog perfusion method. Its repeatedly found concentration in the serum of beeves was 240  $\mu$ gm.

*Human cerebrospinal fluid:* Fluid obtained by lumbar puncture was uniformly inactive (8 specimens), except in one case of arachnoiditis (Foster, Mar. 23) where a 40 per cent concentration in the test bath produced an almost anaphylactic response. Fresh cisternal and ventricular fluid, however, when

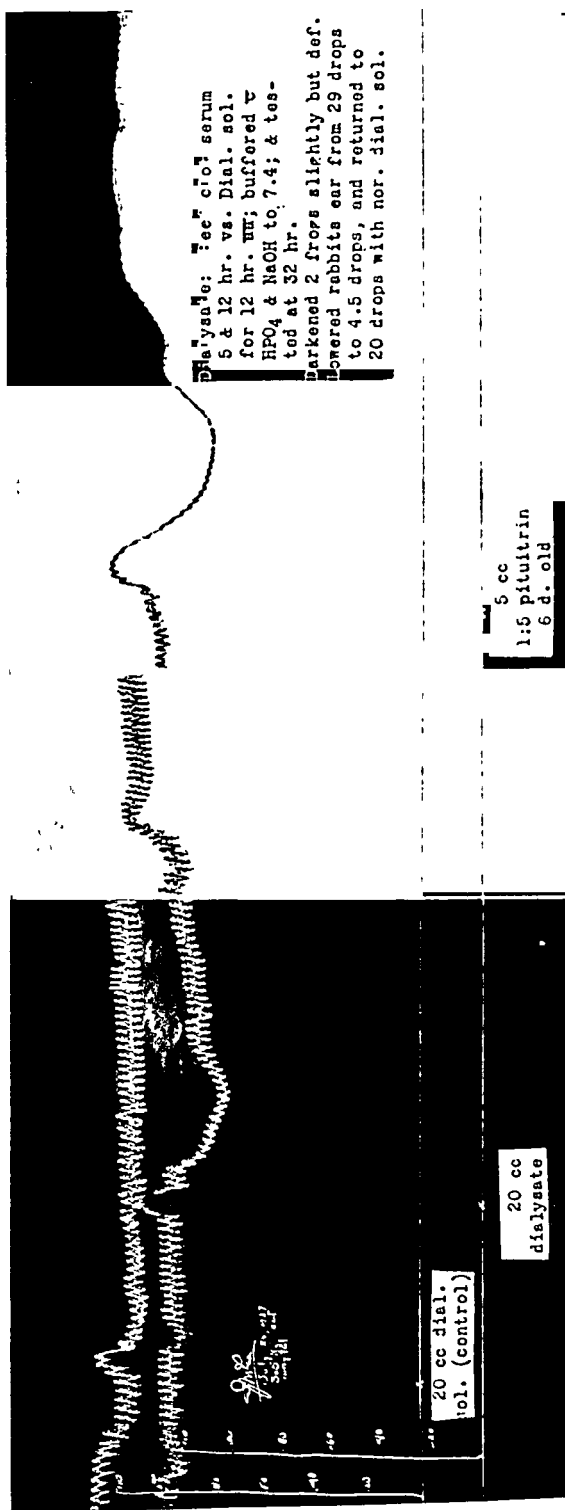


Fig. 5. Haemodynamic action of dialysates of beef clot serum on an amytalized cat. Although there is a considerable depressor action in response to dialysate (about one-third of the duration of depressor action is omitted, for reproduction), the ultimate response is a fairly definite increase in blood-pressure; the dialysate was isotonic with mammalian blood. Dialysing fluid alone produced no response. The records are from the same cat.

obtained from patients without general anaesthesia contained from 25  $\mu$ mgm. to 240  $\mu$ mgm. per mil (5 specimens). Ventricular fluid from etherized patients produced either no contraction or else actual inhibition (7 specimens). In one case, fluid was obtained fractionally on three successive days by cisternal or lumbar puncture from the same patient (Gherardi, May 3-5), who had a retarded absorption of cerebrospinal fluid probably due to a thrombosed and canalizing posterior sagittal sinus following extirpation of a parasagittal meningioma; all were abnormal fluids, in that they foamed when bubbled with oxygen in the titrating bath. The first fluid was obtained by lumbar puncture and consisted of four fractions of 32 mils each; they showed respectively 90, 25, 50, and 0  $\mu$ mgm. per mil. The following day an occipital horn puncture was done, yielding 4 fractions of 22 mils each: 20, 20, 15, and 15  $\mu$ mgm. per mil. The third day 115 cc. was obtained in 5 fractions by lumbar puncture: 25, 10, 7, 7, and 5  $\mu$ mgm. per mil. Attempts to store pooled cerebrospinal fluid in refrigerated glass stoppered brown bottles, after acidulation to 0.25 per cent with acetic acid, were unsuccessful, such fluid showing only depressor action after 40 days. Canine cerebrospinal fluid in 50 per cent concentration produced considerable darkening of frog's melanophores, and immersion of an oxytocic preparation in dogs' 100 per cent cerebrospinal fluid effected an assay of 50  $\mu$ mgm. per mil.

*Pressor activity:* Warmed unconcentrated fresh beef serum dialysate when introduced intravenously into an amygalized cat produced haemodynamic changes similar to those of pituitary extract, and unlike injections of plain dialysing solution (Fig. 5).

#### CHEMISTRY

*Dialysate:* A few miscellaneous color tests were done on the fresh water-clear unsterile dialysates of canine and bovine blood. The membranes used for dialysis were the 6 per cent collodion in 15-85 alcohol-ether, prepared as described above. The biuret test was very faintly positive only on strong alkalization with solid KOH. Saturation in the cold with solid ammonium sulphate produced no demonstrable precipitate in one hour. Half-saturation with phosphotungstic acid, ethyl alcohol,

or picric acid produced a very faint turbidity. Heller and xanthoproteic tests were faintly positive. Ehrlich's diazo reaction gave a flash of pink and red into yellow, and then a slow shading into deep amber; this reaction was not given by pituitary powder extract. Guggenheim's test was negative. While not exhaustive, one may infer from these tests that small amounts of a protein, probably a primary proteose, accompany the active substance of the dialysates.

*Attempts at isolation by Abel procedure:* Abel (1) has reported a method of isolation yielding 0.175 per cent of impure solid "pituitary tartrate" of high physiological activity from posterior lobe substance. Although realizing that in blood the initial concentration per gram is probably some 200,000 to 1,000,000 less than in the material with which he worked, it was nevertheless hoped that a fraction of a milligram sufficient for physiological demonstration might be obtained from large amounts of sera. This obviously would entail "washtub chemistry" at the start, but it was nevertheless carefully and exactly carried completely through on four samples,  $1\frac{1}{2}$  liters of canine serum, and 4000, 4250, and 6000 mls of bovine serum, yielding eventually 82 mgm. of a finely granular tartrate, after 4 treatments with alcoholic picrolonic acid; this, dissolved and reduced to a pH of 7.4 was found to be inactive on guinea pig uterus<sup>3</sup> and on a frog melanophore preparation. By testing the material at various points in the process, both by melanophore and oxytocic methods, it was found uniformly to be present in detectable quantity until after the second phosphotungstic precipitation.

*Concentration:* To test the diuretic effect of pituitrin it must be in such high concentration for injection that both a water and a salt diuresis can be excluded. By vacuum distillation at 15 mm. Hg and 20° C., it was possible to concentrate beef serum dialysate (pH 8.3) 30-fold in 8 hours, while increasing its oxytocic activity 6 times per unit volume. This was not carried further, since the inevitable salt concentration obscured the interpretation of diuresis produced.

#### DISCUSSION

The pertinence of any discussion of route of absorption or excretion of a substance depends first upon recognition and proof of its identity. Chemically, pituitrin is an unknown substance; it has no known specific color reactions other, possibly, than the crude Guggenheim (24) reaction. Physiologically each individual effect of pituitrin may be duplicated by other substances, but the aggregate of its physiological actions (2, 27) is

\*"Salt" contraction a slow, unbroken rise to a plateau, with death of the preparation

fairly specific. Perhaps the nearest approach to a single delicate and specific test known at present, whether chemical or physiological, is the reversible anuran melanophore reaction; it urgently needs further study, however, particularly with protein split-products.

The substance dealt with in the dialysates appears to be pituitrin because it produces quantitative contractions of the guinea pig uterus, darkens the anuran skin reversibly, produces haemodynamic action similar to pituitrin, is not histamin, has its highest known concentration in the external jugular vein, almost disappears from the blood after "complete hypophysectomy" (discussed below), is increased under presumptive hypophysial stimulation through experimental acute hydrocephalus, and increases markedly after starvation. Against these it may be urged that the present dialysates unquestionably show minimal amounts of probable primary proteose (cerebrospinal fluid also contains traces of protein); and that the guinea pig uterus is the preparation par excellence for study of allergic and anaphylactic phenomena (16). Furthermore, many titrations reported in this paper show active substance unmistakably in higher concentration in the femoral vein than in the femoral artery, leading to warrantable suspicion that one may be dealing not with an endocrine substance but with an unknown metabolite. An item of amphoteric value is that with the dialysing membranes described the active substance is found in substantially equal concentration in mixed arterial and venous bloods of dogs, beeves, and men.

Criteria for experimental hypophysectomy, particularly in relation to such a problem as this, warrant more detailed examination (4) than they have usually received. Just as the diabetes-insipidus-adiposo-genital-dystrophy has been split off (8, 5) from the experimental pituitary deficiency picture (14) and assigned to the tuber cinereum, diabetes insipidus, at least, has recently been rationally reclaimed from the tuber cinereum to the pars tuberalis (3) on anatomical and physiological grounds. In canine hypophysectomy, even by the relatively aneurotraumatic transbuccal route, a wide carpeting of pars tuberalis (Fig. 4) is left on the ventral floor of the third ventricle, together with sufficient infundibular stalk tissue to allow later functional re-

placement of the hormone. If destruction of this tissue is attempted mechanically, chemically, or by electrodesiccation, warrantable objection is made that tuber cinereum injury may have been inflicted. Whether operative dexterity can yet overcome this difficulty remains to be seen. At least the old histological criterion of absence of demonstrable eosinophilic pars anterior cells is no longer a valid criterion of a functionally complete hypophysectomy. All laboratory animals examined have this dorsad pars tuberalis flange; it is present even in *Macacus rhesus*

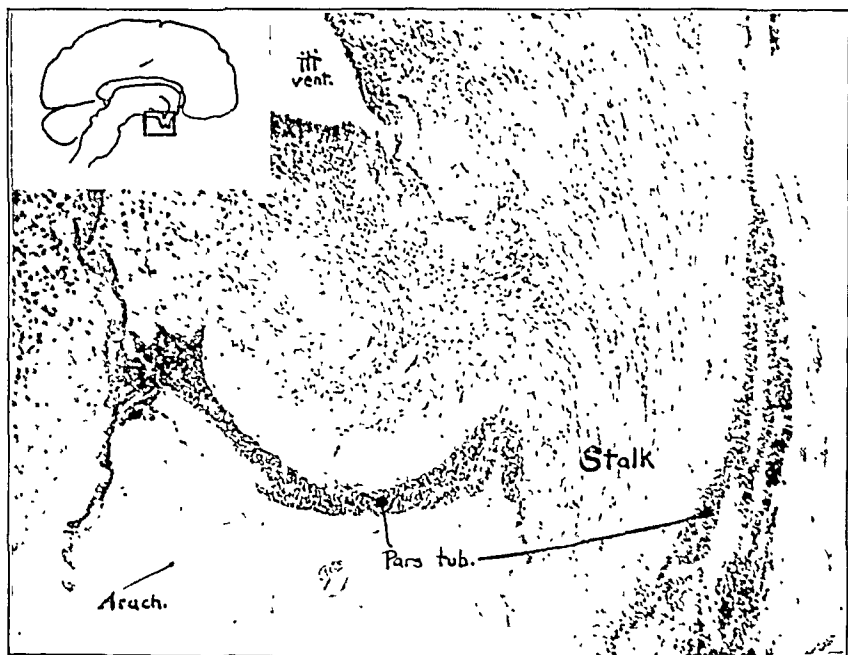


Fig 6. Photomicrograph of sagittal section of infundibular stalk region of *Macacus rhesus*, to show that in the monkey, as well as in the dog and cat, pars tuberalis cells are intimately adherent to the floor of the third ventricle and tuber cinereum. The arachnoid is suggested in the section; it is probable that a surgical mechanical removal would not obtain more than is at present missing, and that pars tuberalis cells and a nubbin of stalk tissue would be left. Other sections show that pars tuberalis extends laterally and posteriorly about one millimeter. The rectangle in the small sketch in the upper left hand corner shows the area enlarged in the photograph.

(Fig. 6), although evidently poorly developed in the normal animal. Search of serial sections of the hypophysectomized animals under report fails to show identifiable pars intermedia cells remaining; especial note should be made (25, 34) that presumptive pituitrin returned to normal concentration in blood and cerebrospinal fluid in the demonstrable absence of these cells—which, however, are probably definite secretory organs (33).

The detection of oxytocic activity in extracts of tuber cinereum after "hypophysectomy" has led Abel (2) to postulate an accessory tissue, producing hormone, in the tuber cinereum, but one might, however, with equal justice urge that the activity which he found was due to transneurally migrating hyaline.

Cogent doubt as to the unitarian nature (2, 32) of the active principle has recently been expressed (20, 30). Regular quantitative, and parallel differences in assay of both standard and unknowns were herein found by oxytocic and melanophore methods (37). This might be due to (a) two autacoids, (b) to actions of different parts of one autacoid molecule (32), or (c) to presence of a depressor substance (40) in both standard and unknowns, effective on the melanophore, but not the oxytocic, preparation; this latter hypothetical substance, however, could not be appreciable histamin, since both Pauly and diazo tests on the standard were negative. Mention has been made heretofore of the single instance in which a dialysate, after standing 54 hours in a refrigerator, was found to be inactive on guinea pig's uterus, although exhibiting enough activity on the melanophore preparation to allow apparently accurate qualitative differentiation. Moreover, the type of oxytocic contraction given by acidulated extracts of the fresh lobe, and of the standard powder, differ; the fresh lobe extract apparently may be added until a threshold is reached, and the uterus immediately spring into nearly maximal contraction with only one or two pauses on the up-stroke, while with powder and dialysate the usual type of curve is a less declivitous ascent interrupted by many rapid hesitations (Fig. 3).

If it be granted for the moment that the active substance or substances dealt with in the present paper are the product of the posterior lobe of the hypophysis, a blood-borne, rather than transneural, route of absorption emerges. This is based largely on two findings: (a) the concentration of presumptive pituitrin is always higher in the external jugular vein than elsewhere in the body, while that of cerebrospinal fluid is less than, or approximates, that of arterial blood; (b) after "sequestration" of the third ventricle (third ventricle choroid intact, however), concentrations in blood and cerebrospinal fluid remain unaffected. Against such an idea may be brought: (a) the proved

fact that lumbar cerebrospinal fluid is almost universally found wholly inactive (6, 41) except in parturient women (49) and in the single arachnoiditic fluid reported herewith, while cisternal and ventricular fluids are in contrast invariably active; and (b) that the concentration of presumptive pituitrin is herein frequently found to be greater in the femoral vein than in the femoral artery.

### SUMMARY

Quantitative physiological evidence (uterus and melano-phore assays) is adduced that presumptive pituitrin is present not only in canine, bovine, and human blood plasma and cerebrospinal fluid, but that it is probably initially absorbed from the gland into the body solely by a vascular route. The detectible substance behaves as if it were at least two entities, is diminished by major infective processes, and starvation, and is increased during anabolic processes.

It is a stimulating debt to acknowledge Dr. Harvey Cushing's constant criticism and suggestion during the progress of this work; it should be added, however, that he is not wholly in accord with the views expressed in the summary above. The kindness of Dr. Stanley Cobb has furnished the Macaque brain, and that of Dr. Blythe Eagles the pure ergothioneine used.

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# THE TECHNIC OF GLAND TRANSPLANTATION

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During the past ten years I have contributed many articles on the various effects of gland transplantation. Because of the simplicity of the operation, however, the operative technic was not discussed in detail. Recently, the number of requests received from surgeons from different parts of the country asking for a description of the technic of the transplantation, make it seem desirable to present the subject more fully so that the operation can be performed by others.

In past articles I have taken up "The indications for gland transplantation" and the subject of "Blood grouping between animals and man." I have discussed the kind of individual in whom the gland transplantation is contraindicated, the time and period it takes a transplanted gland to be absorbed, and have gone into detail on the temporary and lasting effects which might be expected. The reader, therefore, who has followed these articles, which have been based on over five hundred gland transplantations personally performed, is in a position to know whether or not he desires to transplant glandular substance from an animal into one of his patients.

In reference to the actual technic, we may take up the details in the following order:

1. The kind of an animal from which to secure gland substance;
2. Age of animal which gives the best results;
3. Methods of securing the gland;
4. Technic of the operation itself;
5. Post-operative care of the patient.

*The kind of an animal used for gland transplantation:* It is well known that Voronoff prefers to transplant glandular tissue from the anthropoid ape. Others have used glands from goats, and Stanley of California, who adheres to the ram, tried

the human testicle without better results. I have used glands and gland sections from the ram, the sheep, the pregnant cow and the young bull. From my experience with these animals, I prefer the sheep and the ram. Also from experience in transplanting in the human subject, sections of thyroid, sections of prostate, whole ovaries and sections of testicles, and in animals sections of pancreas, I find that sections of testicles and whole and split ovaries give the best results and are less liable to be associated with post-operative sloughing or severe protein reaction.

*The age of the animal:* There are certain classes of patients, women who have had ovariectomies, and men who have become eunuchs from disease, destruction or removal of their testicles, who do not have very lasting effects from transplantation. These cases require repeated transplantations, and I find that the use of the young animals gives much more lasting results than the use of the gland from the mutton.

*Method of securing gland:* In my researches the New York laboratorian of Armour & Company has been an invaluable aid, both in selecting the proper kind of an animal and securing healthy glands for transplantation. Anyone deciding to transplant glandular tissue should endeavor to get in touch with a properly qualified laboratorian to assist in this part of the technic, which is very important. Early in my transplantation activities, Dr. Herman Sharlit, associated with the Roosevelt Laboratories, studied with me the cause of necrosis of gland tissue following a transplantation. We came to the conclusion that this frequent necrosis was due to air-borne bacteria. At that time, I had been securing the glands from the animals in a sterilized thermos bottle containing a warm saline solution, relying on after-sterilization of them to destroy any air bacteria that might collect. We found that the glands became necrotic within twenty-four hours and were loaded with air bacteria. I therefore had the technic of obtaining them changed, and they were brought to me from the slaughter house in a sterilized thermos bottle containing a warm glycerine solution. This cut down the percentage of air bacteria 90 per cent. Later the thermos bottle was sterilized and filled with glycerine solution to which ice washed with ether was added. This seemed to

eliminate the air bacteria entirely. Unfortunately, however, glands frequently underwent necrosis. The technic was again altered to that to which I now adhere with very satisfactory results. A thermos bottle is thoroughly sterilized and taken to the slaughter house. The animal is prepared as usual. Blood from one of the carotid arteries is aspirated into the thermos bottle. The glands to be transplanted from this animal are then allowed to sink into the blood. The thermos bottle with its contents is immediately brought to the operating room. The blood is not clotted when it is received. The glands are removed from the bottle and placed in a five per cent solution of acriflavin, which is kept at a temperature of 105° F. for one hour. The patient is on the table with the abdomen sterilized, awaiting operation.

*The technic:* The technic of the operation for the two sexes is different only as far as the treatment of the gland is concerned. At this point, I should like to repeat a statement that I have made many times before, namely, that the name of *ovarian and testicular transplantation is really a misnomer*. The operator should keep in mind during the entire operation, *that it is a grafting of the skin to the tunics of the ovary or to the tunics of the testicle*. This will better be understood when the next several paragraphs are read.

The transplantation of the ovary will first be described. After novocainizing an area of skin of about three square inches on the abdominal wall with a two per cent solution of novocain containing one cc. of adrenalin chloride to the ounce (I usually transplant in the right or left iliac region), a transverse incision is made across the center of the novocainized area. This incision goes through the skin only and should be about three-fourths of an inch in length. An undercutting knife is then used to make a pocket one and one-half inches square above and one and one-half inches square below this incision, and it should be immediately under the skin; in fact, so close to the skin does the knife adhere that no areolar tissue is left next to the dermis, hence the entire under surface of the dermis comes in direct contact with the gland tunics. One or two ovaries are now removed from the acriflavin solution and are so bi-sectioned that the organ may be opened like a book. Any blood clot or blood from the wound is next cleared away and a fine ocular needle

threaded with fine silk is passed into the pocket from its upper margin. The needle then passes out of the wound through the tunics of one side of the gland, back again into the pocket, up through the skin and out to the surface of the abdomen. A parallel suture three-quarters of an inch away from the entrance of the first is passed through the skin, out through the pocket and through the tunic of the other side of the gland and back the same way as the first. These two sutures are now pulled by the surgeon holding two pair of sutures within his thumb and index finger. This pulls the gland into one of the pockets of the wound and as they are tied on the surface of the abdomen, the tunics of the gland are sutured to the under surface of the dermis. If the symptoms in the case indicate that two glands should be transplanted, the same procedure is repeated, using the lower pocket. The necessity is emphasized of making these pockets of sufficient size to permit the complete disappearance of the transplanted tissue so that none of it lies immediately beneath the wound. The reason for this is that the gland contains a trypsin-like substance, and if any of the gland tissue lies immediately beneath the incision this enzyme will digest the marginal tissue and keep the wound open for a considerable period of time. The wound is now closed with two subcuticular sutures, a deep subcuticular suture composed of silk and horsehair called "Cutis," and a subcuticular suture going through the epithelium only, of horsehair.

When transplanting testicular tissue, the same area is novocainized. An incision two and one-half inches wide is then made transversely across the top of this area and the pocket extends three inches below the inferior border of the wound and is three inches square. A section of testicular substance two and one-half inches square and about one-quarter of an inch thick is now cut from the lateral surface of a healthy ram's testicle which has been sterilized as detailed in case of the ovary. The tunica externa is stripped from this section, but the remaining tunics are left adherent to the substance of the transplant. This section is now deposited in the pocket, sutured to the under surface of the dermis in the same manner as described for the ovary, and the wound is closed in a similar way.

*Post-operative treatment:* The patient is allowed to leave the operating room at once and instructed to keep an ice-bag

over the wound for twenty-four hours. If the patient is compelled immediately to resume his occupation, a small elongated ice-bag similar to that which is used in throat cases may be worn beneath the clothing. After the wound has been sutured, the edges are wiped with iodine and alcohol and dusted with a powder of thymol iodide. A small strip of gauze is now placed over the wound and attached to the skin at each end with collodion, care being taken that the collodion does not touch the edges of the wound. The patient is instructed to return each day for observation and dressing. The dressing consists simply in repeating that which is done at the termination of the operation.

The patients usually have a slight febrile reaction from within twenty-four to forty-eight hours. Rarely does this reaction require any attention. In over five hundred cases in my experience only three ran a temperature of over 103° F. In such cases, five grains of aspirin with an ounce of whiskey every three hours, and a colon irrigation seem to be sufficient.

In from four to seven days the sutures may be removed. Several different reactions may be observed. First, the wound may heal by first intention with very little congestion. Second, the wound may become congested and expel some necrosed gland tissue. Seldom, however, does the whole gland undergo necrosis. After this necrotic tissue is expelled, the wound takes two to three weeks to heal on account of delayed fibrosis between the wound edges. Rarely, the whole gland becomes necrotic and is expelled.

The first indications of a successful result of the transplantation is the return of natural vigor. Patients will inform the surgeon that they are sleeping better, that they feel more rested in the morning than formerly, that they feel more like walking and exercising, and that their appetite is markedly improved. Then other indications of general well-being start to manifest themselves, such as return of libido in men, power of erections, more regular bowel movements; the special senses become more acute, and memory as well as mental concentration improves. The blood pressure, blood chemistry and semen, formerly below normal, show a rapid return to normality. The details of the results of gland transplantation I have of course taken up in former articles.

# THE ANTIDIURETIC EFFECT OF PITUITARY OXY- TOCIC AND PRESSOR PRINCIPLES ON WATER DIURESIS IN MAN

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Since Kamm (1) and his co-workers succeeded in separating the extract of the posterior pituitary body into two almost pure fractions, the oxytocic and pressor, renewed interest in the physiology of this organ has been stimulated. These authors observed in rabbits that the diuretic action of pituitary gland extracts was limited to the pressor principle. Gargle et al. (2) studied the effect of the oxytocic and pressor principles on water diuresis in four normal subjects and on thirst and polyuria in two cases of diabetes insipidus. They also found that the antidiuretic effect was possessed by the pressor principle alone.

Recently, I had occasion to observe the effect of the oxytocic and pressor principles of the pituitary gland on water diuresis in a group of healthy adult male medical students. The materials employed were supplied by the manufacturers, Parke, Davis & Company, under their trade names, Oxytocin and Vasopressin.

The water diuresis test consists of the administration of from 500 to 1500 cc. of water by mouth after emptying the urinary bladder, and then the collection, separately, of all the urine excreted at one hour intervals thereafter. Ordinarily, all the water ingested is excreted in four hours. In the experiments recorded below, 1000 cc. of water was administered in each case save for the exceptions noted. In all, twelve subjects served in the experiments. These were divided into three groups of four each. Group I served as control, unmodified water diuresis test. Group II received in addition to the water, orally, 1 cc. (12 units) of oxytocin, intramuscularly, during the course of the water ingestion. Group III received 1 cc. (12-20 units) of vasopressin, intramuscularly, while ingesting



the water assigned to them. Groups I and II experienced no discomfort during the ingestion of water nor during the remainder of the experiment, whereas Group III had in each case difficulty in drinking the full 1000 cc.; only one succeeded in taking the full amount, and he promptly regurgitated 200 cc. The members of this group experienced other discomforts which are recorded below.

CHART I  
CONTROL GROUP

Urinary volume cc.

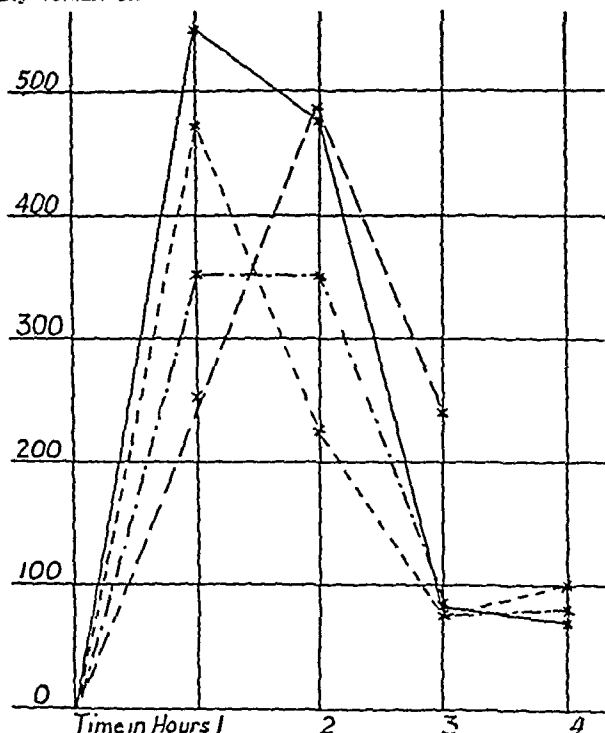


Chart I. Control group. Each member received 1000 cc. of water, orally, and urine specimens were collected hourly. Abscissas, time in hours. Ordinates, volume of urine excreted, in cc.

In order to construct comparative charts for the three groups, the procedure was essentially the same in each case, i. e., all voided before drinking the water assigned to them, all ingested 1000 cc. of water during an interval of 10-15 minutes, save for the exceptions noted; all receiving the pituitary ex-

tracts were injected intramuscularly during the course of the water ingestion; and, with few exceptions, all collected the urine excreted at one hour intervals thereafter. The results obtained in these three groups are recorded in charts I, II, and III, below.

On examination of the three charts, the diuretic effect of water is quite well shown in Chart I; a slight transient retardation of diuresis by oxytocin is demonstrated in Chart II, and a

CHART II  
OXYTOCIN GROUP

Urinary volume cc.

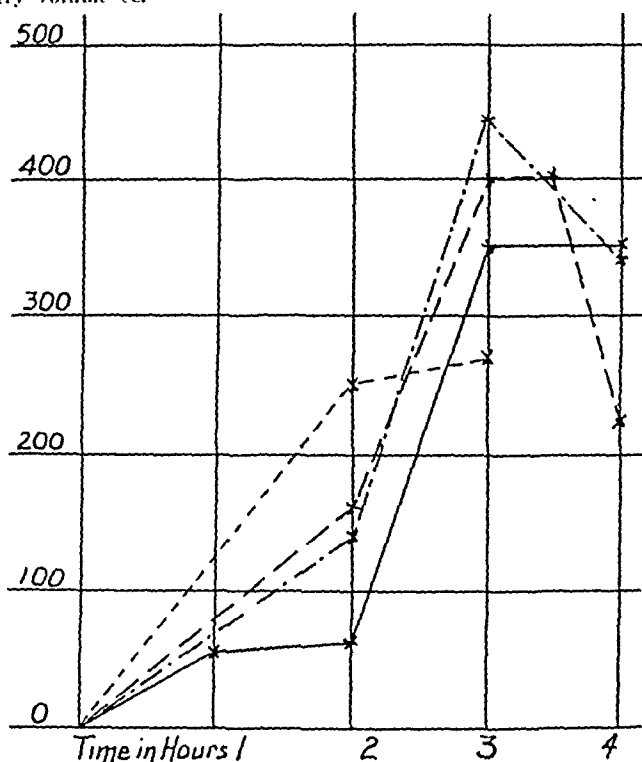


Chart II. Each member received 1000 cc. of water, orally, and 1 cc. (12 units) of oxytocin, intramuscularly. In 3 of the 4 cases here recorded, the first urine collection was two hours after the water ingestion, the other case was one hour after. Abscissas and ordinates as in Chart I.

very distinct and prolonged depression by vasopressin is seen in Chart III. It would seem then that oxytocin has a slight antidiuretic effect. However, in a communication from Dr. Kamm relative to this observation, he calls attention to the fact that the oxytocin supplied has about five per cent of vaso-

pressin as an impurity. This fact can readily explain the result, for he has found that from one to three units of vasopressin have almost as striking an antidiuretic effect as the 12 to 20 units here employed. On this basis, the oxytocin injected contained about a half unit of vasopressin, undoubtedly a large enough quantity to modify the diuresis to the extent observed. From these observations, it is quite clear that the antidiuretic

CHART III  
VASOPRESSIN GROUP

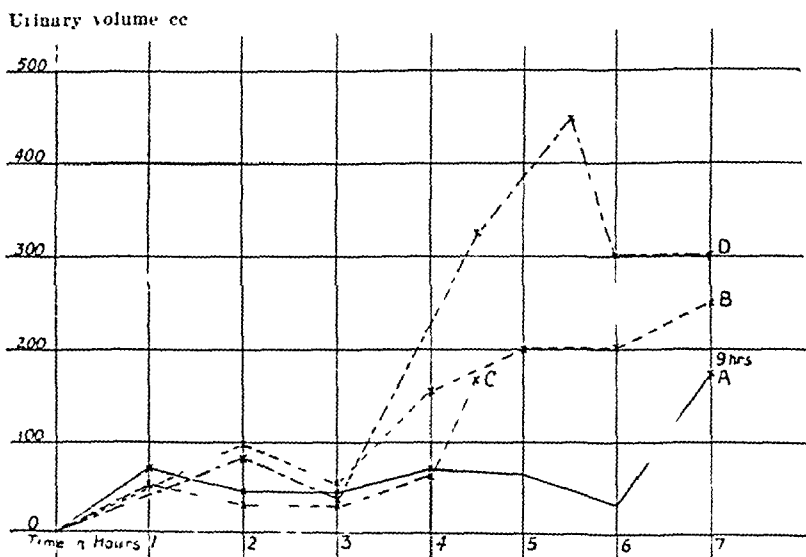


Chart III. A, ingested 800 cc. of water; B, 800 cc.; C, 1000 cc., of which 200 cc. were promptly regurgitated, and D, 725 cc. Each member of this group received in addition 1 cc. (12-20 units) of vasopressin, intramuscularly. A and C voided hourly from the beginning, B and D hourly after the first two hours. Abscissas and ordinates as in Chart I.

action of extracts of the posterior body of the pituitary gland is limited to the pressor fraction. Subject D, in Chart III, shows a diuretic effect following the early antidiuretic effect.

The four control subjects and the four who received oxytocin showed no signs of disturbance due to the tests, and complained of no discomfort. However, the four who received the vasopressin gave evidence of vigorous physiological changes. As mentioned above, one only managed to drink the full amount of water, and he regurgitated 200 cc.; the other three could

not ingest the total amount of water allotted. They all complained of nausea and cramps, and had a prompt bowel movement. These observations point to a stimulation of the smooth musculature of the gastro-intestinal tract as is usually seen after injections of the mixed extract of the posterior lobe of the pituitary gland. These bowel movements were too early to affect the water diuresis tests. All four were very pale for about an hour after the injection.

Vasopressin, then, stimulates the smooth musculature of the gastro-intestinal tract as well as that of the vascular system. The uterus is an organ also composed of smooth muscle, but it responds only feebly to vasopressin and vigorously to oxytocin. Our general conception of the physiological activity of pituitary extract has been that it stimulates all smooth muscle directly. Now, it seems that this conception has to be modified somewhat to explain the reason for the uterus responding in a different manner from other smooth muscles. These observations should serve to open up further experimentation with the object of establishing the mode of action of the extracts of the posterior lobe of the pituitary gland.

#### SUMMARY

Experiments were made on three groups of four each of healthy young men. It was found that the antidiuretic effect of extracts of the posterior pituitary body is due to the pressor principle.

Whereas the oxytocic principle has a vigorous effect upon the uterine movements, it has little if any action on the smooth muscles of the vascular system and of the gastro-intestinal tract.

Vasopressin is the principle which has a pronounced stimulatory action upon the vascular system and gastro-intestinal tract and but a feeble one on the uterine movements.

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# HYPERSENSITIVITY TO INSULIN A POINT OF DIFFERENCE FROM SYNTHALIN AND GLUKHORMENT

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PHILADELPHIA

A married white woman of 41 came to the Diabetic Clinic of The Lankenau Hospital for the relief of distressing occipital headaches preceding and immediately following the menstrual period. These came on, as a rule, in the mornings and lasted several hours. The menstrual cycle was regular each month, lasted five days and was followed by a period of lassitude and weakness.

The patient further complained of an excessive and eccentric appetite, polyuria, with some burning, and also of constipation.

Her past history indicated susceptibility to infections in the upper respiratory tract, causing frequent severe colds, sore throat, and tonsillitis.

The significant features in the physical examination of the patient were moderate obesity (170 pounds), pyorrhea, mild hypertension (184/100) and fasting hyperglycemia of 385 mgm. per 100 cc. of blood. The blood urea was 12 mgm.; cholesterol, 220 mgm. The red cell count showed a mild anemia, the erythrocytes being 3,560,000 and hemoglobin 75 per cent. The leucocyte count was 4,500 with polymorphonuclears, 53; lymphocytes, 40; and large monocytes, 7. Plasma CO<sub>2</sub> was 60 volumes per cent. The Wassermann reaction was negative.

A urine analysis (24 hour specimen) gave a specific gravity of 1.024 and 4.16 per cent glucose. Tests for acetone and diacetic acid were negative.

The patient was given a diet of carbohydrate 70 grams; protein 60 grams; and fat 100 grams; total calories 1420, following a day of starvation. As there was no appreciable effect on the blood sugar after various modifications of the diet, ten

units of insulin three times a day just before meals was prescribed.

Following the first injection of ten units, before breakfast, an erythematous swelling three cm. in diameter developed at the site of injection and the patient complained of weakness, flushes, vertigo, and faintness. Upon reclining for a short time the general symptoms passed away but the local swelling persisted for five days. At noon following another injection of insulin by the nurse the same symptoms reappeared and the attending physician was summoned. A survey of the technique showed a minimal opportunity for factors other than the solution containing insulin to have been the cause of the reaction. Skin sensitization tests using the various preparations of available proteins, including beef and pork, pollens, etc., were made and all proved negative. Four different commercial preparations of insulin were then injected intradermally using one minim of a U-20 strength. Beginning two minutes after injection a blanching bleb appeared at the site of each puncture and gradually enlarged to an area three cm. in diameter. At the end of three hours each reaction had disappeared. Sterile saline was used as control.

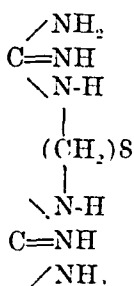
Utilizing the sensitivity of this patient to insulin as a method by which to study possible similarities of insulin, synthalin [of Frank (1) (1a)] and glukhorment [of Von Noorden (2)] an aqueous preparation of synthalin (2.5 mgm. per cc.), and one tablet of glukhorment dissolved in two cc. of phosphate buffer solution, prepared by Dr. Hammett of The Lankenau Hospital Research Institute, further sensitization tests were performed. One minim each of four commercial preparations of insulin (U-20); one minim of aqueous synthalin solution (2.5 mgm. per cc.) and one minim of a phosphate buffer solution of glukhorment (one tablet in 2 cc.) were injected intradermally on the volar surface of the forearm. The glukhorment preparation was controlled by using phosphate buffers pH 8, and pH 6 as controls. Normal saline was again the control solution.

The same reaction once more occurred with insulin as above described; to synthalin there was a very slight blush which faded in two minutes and to the glukhorment preparation no reaction was noted. Blood sugar examinations taken before and after the sensitization tests showed no alteration.

As the present commercial preparations of insulin are now prepared it is unlikely that impurities in the solution would cause the reaction. Joslin (3), Wilder (4), and Geyelin (5) in 1922 reported instances of reaction following injections of the relatively impure preparation, of which at least five cc. had been injected before the disturbance occurred. By refinement in preparation the solutions subsequently marketed contain none of these impurities. On the other hand certain individuals are sensitive even to the insulin as now prepared, if it is given in sufficient amount. In 1926, Walker (6) described a case in which urticaria and edema developed following a week of insulin therapy. Engelberg in 1927 reported a similar type of case. Differing from the case herein described, modification of dosage eliminated further reactions and the patients continued the insulin. Recently Tuft (7) has recorded another case of a patient who became hypersensitive to insulin after several months of insulin therapy. This patient, likewise, showed a generalized rash and swellings of the extremities following insulin.

Abel (8) and his co-workers have found that each unit of insulin contains 0.006 to 0.01 mgm. nitrogen.

In contradistinction to insulin products, synthalin is a synthetic guanidine derivative with the formula:



Glukhorment was originally described as a product obtained by the fermentation of endocrine glands until glycoeyanin results. But recent researches by Bischoff, Blatherwick, and Sahyun (9) have shown that glukhorment also contains a guanidine derivative which, they state, "is either synthalin or a near homologue of it."

Note should be made that the patient herein described was

unable to take synthalin orally, suffering from nausea and vomiting each time a tablet was given, a disturbance frequently provoked by this drug. Glukhorment was not given by mouth.

#### SUMMARY

A brief case report is made of a female patient showing immediate local and systemic reaction to injection of insulin. Comparative intradermal tests with an aqueous solution of synthalin and a phosphate buffered solution of glukhorment gave no local or systemic reaction.

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# Abstract Department

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**Influence of suprarenals on blood pressure regulation (Influencia de los glandulas suprarenales sobre la regulacion de la presion arterial):** Biasotti, A., Thesis. National Univ. of Buenos Aires. 1927.

The author's aim was to secure experimental evidence under purely physiological conditions and without the perturbing effects of anesthetics and operations. The blood pressures were measured on the femoral artery by the indirect method and with the precaution of avoiding emotional hypertension. Extirpation of one or both of the abdominal chains and the splanchnics was without effect upon the blood pressure. Removal of one adrenal was equally ineffective. If, however, the second adrenal was removed, and the dog died within 20-60 hours, the blood pressure fell rapidly. Removal of one adrenal and demedullation of the other was followed by a hypotension of 3-4 cms., which finally disappeared after 20-30 days. The recovery was not due to proliferation of chromafine bodies nor to the abdominal sympathetic chain. Reactivity to hemorrhage amounting to 1.5 per cent of body weight was found to be much more marked and prolonged (2-5 cms. fall prolonged for three hours) in dogs whose blood pressure had recovered after adrenal demedullation than in controls (1-2 cms. fall that disappeared after an hour). The author concludes that the main role for re-establishing the blood pressure to the normal level corresponds mainly to the vasomotor apparatus, while that of adrenal secretion is only secondary and accessory.—J. J. Izquierdo.

**Glutathione and the adrenals (Glandes surrénales et glutathion).** Binet, L., and A. Giroud, Compt. rend. Soc. de biol. 98: 434. 1928.

The adrenal is the tissue of the body containing most glutathione. It is the cortex of the glands which is the richer and in young guinea pigs the zona reticularis, which is the richest part of the cortex in this substance.—J. C. D.

**Latent malaria and adrenin (Adrénalino-diagnostic du paludisme latent).** Canciulesco, M., L. Herman and R. Hirsch, Compt. rend. Soc. de biol. 98: 459. 1928.

As the result of the study of twelve cases in which 1 to 2 mgm. of adrenalin in a 1 per cent solution was injected subcutaneously, the authors conclude (1) that it is very helpful in diagnosing latent cases since the organism can now be found in the blood, (2) that no untoward results either due to hypertension or to relighting a quiescent malaria follow, (3) that it may be helpful since the organisms are forced out from the security of the spleen into the peripheral blood loaded with quinine.—J. C. D.

**Temperature control and the adrenals (Rôle des capsules surrénales dans la thermorégulation).** Chahovitch, X., V. Arnovljévitch and M. Vichnjitch, *Compt. rend. Soc. de biol.* 98: 511. 1928.

In normal rabbits injection of milk into the heart was followed by a rise in temperature (rectal). In decapsulated rabbits the temperature fell and the animals died a few hours after the injection.

—J. C. D.

**Primary tumor of the suprarenal capsule with especial reference to adrenal virilism.** Crosbie, A. H. and L. W. Smith, *J. Urol.* 19: 241. 1928.

This is the report of a case in which the tumor was removed at operation.—J. C. D.

**The adrenal gland in pregnancy: cortico-medullary relations on albino rat.** Donaldson, J. C., *Anat. Rec.* 38: 239. 1928.

Measurements by the reconstruction method show that during pregnancy there is no change in the relative volumes of the cortex and the medulla.—Author's Abst.

**Adrenal gland in wild gray and albino rat: cortico-medullary relations.** Donaldson, J. C., *Proc. Soc. Exper. Biol. & Med.* 25: 300. 1928.

Measurements based on the reconstruction method show: (1) The proportion of medullary tissue to cortical tissue is less in the wild gray than the albino, (2) the absolute amount of chromaffin tissue is greater than in the wild gray, and (3) most of the greater mass of the adrenal in the wild gray consists of cortical material.

—Author's Abst.

**Comparative sensitiveness of blood pressure and intestinal motility to epinephrin.** Dragstedt, C. A. and J. W. Huffman, *Proc. Soc. Exper. Biol. & Med.* 25: 241. 1928.

In four dogs to whom neither anesthetics nor drugs were given, a rise of blood pressure without intestinal inhibition in response to epinephrin was observed. Simultaneous records were also obtained

in 6 animals to whom morphine was administered, and in 1 animal to whom paraldehyde had been given. In each of the animals a rise of blood pressure without intestinal inhibition was obtained. Epinephrin was injected intravenously by means of a Woodyatt pump for two to ten minutes. In every instance a sufficient dose of epinephrin was effective in maintaining intestinal inhibition.

—M. O. L.

The hemodynamic action of minimal effective doses of epinephrin in the unanesthetized dog. Dragstedt, C. A., A. H. Wightman and J. W. Huffman, *Am. J. Physiol.* 84: 307. 1928.

In 16 unanesthetized dogs adrenalin was injected by vein and blood pressure recorded from a transposed carotid artery. Contrary to the results of previous investigations on anesthetized dogs (and various clinical observations on unanesthetized patients) it was found that the minimal effective dose of epinephrin on sustained administration in the unanesthetized dog produces pressor effects. The minimal effective dose of epinephrin in such animals is less than from 0.2 to 0.4 cc. of a 1 to 1 million solution of adrenalin per kgm. per minute.—R. G. H.

Effect of intramuscular injections of adrenin on the gastrocnemius of a decapsulated frog (*Effet de l'injection intramusculaire d'adrénaline sur la contractilité du gastrocnémien de la grenouille surrénalisée*). Ferreira, de M., *Compt. rend. Soc. de biol.* 98: 467. 1928.

Such injections have little effect. The recuperation of muscles from fatigue which follows injection of adrenin into the dorsal lymph sac is, therefore, due to a central action and not a direct action on the capillaries of the muscle.—J. C. D.

XVIII. The depressor effect of epinephrin in decerebrated animals. Gruber, C. M., *Am. J. Physiol.* 84: 345. 1928.

Experiments were made on 8 cats. The animals were decerebrated under ether and adrenalin injected intravenously from  $\frac{1}{2}$  to  $3\frac{1}{4}$  hours later. It was found that epinephrin in small doses caused a fall in blood pressure. Decerebration did not alter the vasomotor response in skeletal muscle. Decerebration heightened the vasoconstrictor action of epinephrin. Epinephrin, when injected intravenously in decerebrated animals frequently caused vasomotor variations to an extent not commonly observed in anesthetized cats.

—R. G. H.

The effect of neurine and ephedrine on the secretion of adrenin (*Action de la neurine et de l'éphédrine sur la sécrétion d'adréna-*

line). Houssay, B. A. and E. A. Molinelli, *Compt. rend. Soc. de biol.* 98: 172. 1928.

Both substances cause a discharge of adrenin but the rise in blood pressure following injection of neurine or ephedrine is not dependent on this discharge. The conclusions are derived from experiments on dogs.—J. C. D.

The size relations of the human adrenal during foetal life (*Die Grössenverhältnisse der Nebennieren im Laufe des Fötallebens des Menschen*). Jonsson, E. and N. Aderman, *Upsala Läkaref. Förh.* 32: 381. 1927.

One hundred and one normal foetuses from four months to birth, obtained from normal mothers and fixed in formalin, were examined. A steady enlargement of the gland, as shown by tables and graphs, takes place until almost the time of birth. Growth stops then to be continued post-partum.—J. C. D.

The chromaphil tissue and the interrenal bodies of *Elasmobranchs* and the occurrence of adrenin. Lutz, B. R. and L. C. Wyman, *J. Exper. Zool.* 47: 205. 1927.

The two adrenal representatives can be separated without contamination from one to the other in *Squalus acanthias*, *Raja stabuliformis*, *Raja diaphanes* and *Raja erinacea*. Ringer extracts of interrenals, chromaphil bodies and gastric ganglia were tested by the mydriatic method for the presence of a dilator substance. The interrenals of all four species were negative for a dilator substance and the chromaphil bodies were positive. Extracts of gastric ganglia from *Squalus* were positive, from *Raja diaphanes* and *Raja erinacea* negative, and from *Raja stabuliformis* sometimes negative and sometimes positive. Extracts of accessory gastric ganglia from *Raja stabuliformis* were sometimes positive and sometimes negative. All physiological tests were correlated with the presence or absence of chromaphil tissue as seen in sections stained with bichromate. It is concluded that the interrenals of *Elasmobranchs* do not manufacture or store adrenin. The homology of this gland with the cortical tissue of the adrenal gland of the higher vertebrates leads to the conclusion that cortical tissue does not make adrenin.

—Authors' Abst.

Adrenaline vaso-motor dilation. Macdonald, A. D. and W. Schlapp, *J. Physiol.* 62: 12. 1926.

Small doses of adrenaline (0.002 mgm.) may depress the blood pressure of the anaesthetized cat, and various explanations have been given for this phenomenon. It does not appear to have been realized or appreciated that this fall of pressure is very specially

related to the anaesthesia; it is marked under ether and urethane, less marked under chloralose if no ether has been given just before.

In the decerebrate cat from which all traces of ether have been thoroughly ventilated and after the circulation has had time to recover from the effects of anaesthetic, no such depressor response can be evoked, although it was well-marked shortly after decerebration and the level of blood-pressure remains scarcely changed. Depressor doses may now produce prolonged and considerable rises, often interrupted by a notch suggesting a double seat of action of the drug. On ether being supplied to such an animal the depressor response quickly returns. If, as Burn and Dale suggest, adrenaline vaso-dilation be due to the production in the lungs of minute amounts of a histamine-like substance, that substance can only be produced or liberated under the influence of the anaesthetic, for the blood-pressure response to small doses of histamine itself is little affected by the nature or degree of the anaesthetic in an animal with high blood-pressure.—Authors' Abst.

**Enlargement of the adrenal cortex**<sup>\*</sup> in experimental uremia. MacKay, E. M. and L. L. MacKay, J. Exper. Med. 46: 429. 1927.

After the removal of both kidneys in rats there was an hypertrophy of the adrenal cortex amounting to 45 to 65 per cent. There was no change in the medulla.—M. O. L.

**Suprarenal tissue in the food of mice.** Effects on the development of the organism and on the sexual function (*Le tissu surrenal dans l'alimentation des souris. Effects sur le developpement de l'organisme et sur la fonction sexuelle*). de Mira, F., jun., Arch. portug. des sc. biol. 2: 84. 1927. Abst., Physiol. Absts. 23: 107.

Feeding suprarenal tissue to mice produces hypertrophy of the testicles, increased muscular activity and pugnacity.

**Addison's disease in association with amyloidosis.** Philpott, N. W., Ann. Int. Med. 1: 613. 1928.

Review of 2550 autopsy cases in the University of Michigan Hospital revealed 14 of definite Addison's disease. The associated conditions were tuberculosis, 7; carcinoma metastases, 4; mycosis fungoides, 1; simple atrophy, 1; and amyloidosis, 1. The case of amyloidosis, which is here described, gave a clinical picture of typical Addison's disease. Microscopic examination showed both adrenals almost completely replaced by amyloid, more marked in the medulla and inner portion of the cortex than at the periphery. The semi-lunar ganglia were involved also. There was a generalized amyloidosis which was thought to be due to an old pulmonary tuberculosis. There was no tuberculosis of the adrenals.—Author's Abst.

Studies on adrenal insufficiency. IV. The influence of intravenous injections of Ringer's solution upon the survival period in adrenalectomized dogs. Rogoff, J. M. and G. N. Stewart, *Am. J. Physiol.* 84: 649. 1928.

Marked prolongation of the survival period or the period of good health was caused in adrenalectomized dogs, by daily intravenous injection of Ringer's solution (generally about 100 cc. per kgm. of body weight). Dextrose was almost always added. A table is given showing results on 17 animals. One lived 13 days, 15 hours; one 14 days, 4 hours; one 14 days, 20 hours; one 15 days, 5 hours; one 17 days, 6 hours; one 19 days, 8 hours; one 19 days, 12 hours; one 20 days; one 20 days, 3 hours; one 32 days, 17 hours; one 33 days, 5 hours; one 38 days, 2 hours; one 53 days, 16 hours. Marked amelioration of symptoms, even when acute, was almost always produced during and immediately following injection. Sometimes animals have been rescued, when already comatose, and have lived a long time in good health. Possible ways in which the injections may act are discussed in the paper.—Authors' Abst.

Studies on adrenal insufficiency. V. The influence of adrenal extracts on the survival period of adrenalectomized dogs. Rogoff, J. M. and G. N. Stewart, *Am. J. Physiol.* 84: 660. 1928.

Dogs subjected to double adrenalectomy were treated by intravenous administration of extracts of the cortical portion of adrenal glands. The criterion adopted to determine the efficacy of the extracts was the effect on the survival period. In a large series of controls the majority of the animals survived about a week to 10 days, a number less than a week. About 8 per cent survived a fortnight or somewhat longer. Among the animals that were treated with adrenal extracts about 25 per cent survived beyond the upper limit observed in the controls (18 to 78 days). Of those that did not exceed the survival period of control dogs many reached, or nearly reached, the maximum survival period. In these, as well as in the animals that survived longer, there was observed amelioration of symptoms and at autopsy the condition of the alimentary canal was found to be much less severe.—J. M. Rogoff.

Chloralose and the secretion of adrenin (Chloralose et adrénalino-sécrétion). Tournade, A. and H. Hermann, *Compt. rend. Soc. de biol.* 98: 306. 1928.

When the adrenal vein of one dog (A) is anastomosed to the jugular of another (B) whose adrenals have been removed, effects of adrenin secretion can be measured by injecting substances into A and measuring the blood pressure changes in B. Such experiments show that chloralose stops the secretion of adrenin for a short time.—J. C. D.

**Adrenin output in peptone shock** (*L'adrénalino-sécrétion au cours du choc provoqué par injection intraveineuse de peptone*). Tournadé, A. and H. Hermann, *Compt. rend. Soc. de biol.* 98: 342. 1928.

Experiments using the jugular-adrenal anastomosis method with dogs proved that there was an initial fall followed by a marked rise in adrenin secretion following intravenous injection of peptone.

—J. C. D.

**The cholin forming properties of the adrenals** (*Fonction cholinigène des surrénales*). Viale, G., *Compt. rend. Soc. de biol.* 98: 177. 1928.

After adrenalectomy there is no diminution of cholin in the blood. The blood of the adrenal vein contains almost twice as much cholin per litre as does the general circulation.—J. C. D.

**The supposed antitoxic action of the adrenals** (*Fonction antitoxique supposée des surrénales*). Viale, G., *Compt. rend. Soc. de biol.* 98: 178. 1928.

The toxic action of the serum from adrenalectomized dogs, when tested on the heart, is not due to toxins which are normally neutralized by the adrenal, but to toxins absorbed from the intestinal tract as the result of the injuries to the mucous membrane following adrenalectomy.—J. C. D.

**The influence of adrenalin and of some other internal secretions on the contractions of skeletal muscle of warm-blooded animals** (*Ueber den Einfluss des Adrenalins und einiger anderer Inkrete auf die Kontraktionen des Warmblüterskelettmuskels*). Wastl, Helene, *Arch. f. d. ges. Physiol.* 219: 337-390. 1928.

Adrenalin injections tend to inhibit muscle contraction, though the limiting concentration before the effect is shown differs for different animals and is in general higher for males than for females (experiments on the tibialis anterior muscle of cats under urethane). Thyroid produces no direct effect, but the effect of adrenalin after thyroid is lessened (as also after pituitary extracts). Histamine appears to have a direct toxic action on these skeletal muscles.

—A. T. C.

**Neuroblastoma of the adrenal in young children.** Wollstein, Martha, *Surg. Gynec. Obst.* 46: 774-782. 1928.

Of nine sympathicoblastomata of the adrenal medulla in young children, three contained areas of ganglioneuroma in parts of the tumor. One had metastasized very generally to the bones, dura, and liver. Seven were inoperable when first diagnosed. The other two were removed by operation before metastases occurred and both children recovered, one being still alive 17 months after operation, a longer period than any previously recorded.—A. T. C.

**Alterations in the homoplastic grafts of endocrine organs** (*Ricerche intese a modificare il destino dell'innesto omplastico di organi a secrezione interna*). Castiglioni, G., *Riforma med.* 43: 387-388, 1927.

Starting from the principles that (1) by sensitizing the grafted animal with serum taken from the giver, the grafts are readily re-absorbed and that (2) by blocking the reticulo-endothelial apparatus the grafts held well, and anaphylactic shock was prevented, the author chose the opposite way and tried to "desensitize" the grafted animals. After the grafting, small doses of extract of the homologous organ were injected into the grafted animal every other day, beginning with the second day after operation. The controls were grafted but not treated afterwards. As a result in the treated animals the grafted ovary, for instance, did not begin to degenerate before 100 to 150 days, while in the controls the destruction of the organ was complete after 50 days. Considering that the chosen animals were not either previously or afterwards deprived of the corresponding organs, the author considers these results as very encouraging. He does not attempt any explanation, but advances the hypothesis that the phenomenon may be due to "desensitization."

—G. V.

**Endocrinological formulae in children at various age periods** (*Über die endokrinologische Formel bei Kindern in verschiedenen Altersperioden*). Fertik, J. M., A. J. Majanz, and S. M. Monossohn, *Jahrb. f. Kinderh.* 115: 363. 1927.

This study is based upon autopsy material of 214 cases in which the weight of the thymus, adrenals, thyroid and pituitary was taken. The pancreas and sex glands were not included, as they have external glands as well. While the results are not definitely conclusive and require further study, the authors were able to show that there are five growth periods, corresponding to birth to 7-8 months, 2-6 months, 4½ years, 7-8 years and 14 years. The findings in the adrenals especially require further study as the growth in boys and girls differ so radically that an average cannot be struck. For girls up to 11 years there is a slow growth with but two zones, 6 months and 4 years, remaining high from the latter period up to the 11th year. In boys, five zones of growth are found. The weights of the thyroid and adrenals show a gradual rise from birth up to the 12th or 13th year. This curve has definite periods dividing it into definite zones. The relation in growth between the thyroid and adrenals at certain age periods is quite pronounced, giving the so-called adrenal-thyroid quotient. The periods are those mentioned above. The pituitary and pineal have similar growth periods.—M. B. G.

**The purification of heparin and its chemical and physiological reactions.** Howell, W. H., *Bull. Johns Hopkins Hosp.* 42: 199. 1928.



A method of extraction and purification of crude heparin is described which gives a product free from phosphorus and nitrogen. The reactions of the purified heparin indicate that it is a carbohydrate derived from glycuronic acid. One milligram of this material is sufficient to prevent approximately 100 cc. of blood from clotting for 24 hours or longer. Solutions are stable and may be sterilized by boiling. The material has been used with good results as an anti-coagulant for blood transfusions.—M. O. L.

**Diagnosis of pregnancy by detection of hormone in the urine (Schwangerschaftsdiagnose aus dem Harndurch hormonnachweis).**  
Ascheim, S. and B. Zondek, *Klin. Wehnschr.* 7: 8. 1928.

Ovarian hormone in the urine does not serve as a biologic diagnosis of pregnancy, as it does not appear in the urine during the first eight or ten weeks. Even later it cannot always be demonstrated with certainty. Besides it occurs in non-pregnant women with functional disorders, especially during the menopause. On the contrary, the determination of the hormone of the anterior pituitary lobe in human urine is of definite value in the diagnosis of pregnancy, especially for early diagnosis. The test is made by injecting 1-2 cm. morning urine into five young mice and the effect upon the ovary established. For control, 4 cm. of urine are injected into an adult castrated mouse. This makes it possible to differentiate between the ovarian and anterior pituitary hormone. An enormous increase of the anterior pituitary hormone in the urine is characteristic of pregnancy. In 16 marked endocrine cases the reaction was slightly positive in three; in two cases of marked myxoedema, and in one case of acromegaly. However, these cases are easily excluded in pregnancy because they are not so prevalent. Cases, especially where there is an increase in the tissue growth, as in pregnancy, were investigated, e. g. carcinoma (22 cases). Reaction was found positive, particularly in carcinoma of the genitals in the female. In round numbers one-fifth of the cases were positive. In 78 cases of pregnancy examined, 76 were positive. The reaction is found positive five days after cessation of menstrual period. The error in these tests amounts to 4 per cent. The technic of the methods will be published in a later article.—H. G. Beck.

**Changes in the urogenital apparatus of the female *Triton cristatus* following testicular grafts (Modifications de l'appareil uro-génital du *Triton cristatus* femelle après greffe de testicules).** Beaumont, J., *Compt. rend. Soc. de biol.* 98: 563-564. 1928.

In this urodele the glandular lining of the tract comes to resemble more nearly that of the male, but no new structures corresponding to male organs are formed.—J. C. D.

The female sex hormone (*Sur les hormones sexuelles de la femelle*). Bencan, C. Champy, and T. Keller, *Compt. rend. Soc. de biol.* 97: 229. 1927.

Water extracts from the corpus luteum, when injected into guinea pigs, produce congestion of the uterus and of the mammary glands. A similar effect is given by water extracts of placenta. This is in contrast to the hormone of Allen and Doisy, which is associated with lipoids and found in the follicular fluid and placenta. The changes in menstruation are due to these two hormones acting consecutively, while those of pregnancy are due to their simultaneous action.—J. C. D.

Over-masculinity in the cock. New evidence favoring the theory of a quantitative action of the sex hormone (*L'hypermasculinisation chez le coq. Nouvel argument en faveur d'une théorie de l'action quantitative de l'hormone sexuelle*). Benoit, J., *Compt. rend. Soc. de biol.* 98: 538. 1928.

In partially castrated males the comb, while slower in growing than in controls, finally attained a greater size. This is evidence that removal of a part of the testes has stimulated the remainder to the production of more hormone than normal and that this hormone acts quantitatively and not according to an "all or none" law. —J. C. D.

Pseudo-pregnancy produced by the persistence of a corpus luteum spureum (*Pseudo-grosses créée par la persistance d'un corps jaune périodique*). Courrier, R., H. Duboucher and E. Pouget, *Compt. rend. Soc. de biol.* 97: 271. 1927.

A woman developed the signs of pregnancy, including suppression of menstruation, enlargement of uterus, and morning sickness. After three months, menstruation reappeared. At operation a mass on the right ovary, mistaken for an extra-uterine pregnancy, was found to be a corpus luteum. No signs of implantation were found. This seems to be a true case of pseudo-pregnancy similar to that found in the rodents and dependent on the persistence of a corpus luteum.—J. C. D.

Is the Allen-Doisy test specific for the female sex hormone? Dohrn, M., *Klin. Wchnschr.* 6: 359. 1927.

The writer asks this question after a study of animal reactions to injections of extracts of plant material.—E. A.

Inhibition of ovulation by the corpus luteum (*Sur l'inhibition de l'ovulation par le corps jaune*). Gley, P., *Compt. rend. Soc. de biol.* 98: 504. 1928.

The author has developed a method (to be reported) of preparing non-toxic corpus luteum extract. Daily subcutaneous injections

in rats caused a suspension of the oestrous cycle, as followed by the vaginal smear, as long and only as long as such injections were continued.—J. C. D.

**Cyclic variations of the sex hormone content of the blood in women** (*Die Schwankungen des Sexualhormongehaltes im Blute der Frau*). Hirsch, H., *Arch. f. Gynäk.* 133: 173-185. 1928.

A brief review of the literature is followed by the author's report on 73 blood determinations in women in various stages of the menstrual cycle. This shows that the hormone is not present in appreciable quantities during the early part of the menstrual cycle. It appears first about the middle of the menstrual cycle. The concentration increases until the onset of the flow, when it falls rapidly until it is barely perceptible the following day. The hormone curve corresponds to the growth curve of the endometrium. In pregnancy, the hormone appears about the sixth week and from that time the concentration in the blood increases until the onset of labor. It is more concentrated in menstrual blood than in the puerperium. Thirteen days after childbirth, the circulating blood is negative for the hormone. Lochia gives positive results for at least 27 hours. Elimination of the hormone from the circulating blood occurs through the menstrual flow and lochia. The placenta plays an important role in the production of the hormone in the latter months of pregnancy. Similarity is noted in the development of the corpus luteum and the increase of concentration of the hormone in circulating blood of non-pregnant women.—J. P. Pratt.

**Concerning female sex hormone, especially Menformon.** Laquer, E., *Munchen. med. Wchnschr.* 74: 2045. 1927.

A review of recent work with especial attention to the author's contributions to the subject.—E. A.

**The female sexual hormone, menformone. VII. The action of the ovarian hormone, especially menformone, administered by mouth, and the importance of its administration in several doses** (*Ueber weibliches Sexualhormon, Menformon; über die Wirkung von Ovarialhormon, im besonderen von Menformon per os, und über Bedeutung der Verteilung der Dosis*). Laqueur, E., P. C. Hart and S. E. de Jongh, *Deutsche med. Wchnschr.* 53: 1583. 1927. *Abst., Chem. Absts.* 22: 617.

The dosage of menformone is 100 times as great when given to rats by mouth as when given subcutaneously. In mice, it is only 11 times as great. The same amount of hormone is much more effective when given in several doses than when injected in a single dose.

**The influence of the internal secretion of the ovary on the calcium blood level and on calcium metabolism.** Mirvish, L. and L. P.

Bossman, Quart. J. Exper. Physiol. 18: 11. 1927. The effect of ovarian extracts on the calcium blood level. Ibid, p. 29.

A method is described for the preparation of ovarian extracts that will produce depression of blood calcium in rabbits, and, in smaller doses, comparable effects in human subjects. The maximum effect occurs in 24 hours, with complete recovery in 48 hours. This effect is suggested as a means of standarizing ovarian extracts. The effect is irrespective of sex.—C. I. R.

The causation of the anoestrous period. Parkes, A. S. and F. W. R. Brambell, J. Physiol. 64: 388. 1928.

In mice a prolonged environmental temperature of about 0° C. has no permanent effect on the anoestrus period except an initial lengthening of the period; from this it is concluded that the prolonged winter anoestrus of wild rodents is due to diminished food supply rather than to lowered temperature.—C. I. R.

Studies on the internal secretion of the ovary. V The oestrus-inhibiting function of the corpus luteum. Parkes, A. S. and C. W. Bellerby, J. Physiol. 64: 233. 1927.

A method is described for the preparation of an oestrus-inhibiting extract. The corpus luteum of ovulation is not the organ of oestrin elaboration. Inhibiting of oestrus and ovulation during pregnancy is only one of several functions of the corpus luteum.

—C. I. R.

The cyclical growth of the vesicula seminalis in birds is hormone controlled. Riddle, O., Anat. Rec. 37: 1. 1927.

Two cases were found in feral birds (oven-bird, wood-thrush) of normal enlargement of both (right and left) vesiculae seminales, although no sperm was or could ever have been present in one of them. This was because of the absence of a testicle in one case, and the dislocation (mesentery) of a normal testis in the other. This cyclical growth, amounting to at least 2,000 per cent, undoubtedly is based on hormone action, probably on that of the testis. It is pointed out that all of the few known cases of marked cyclical growth, antlers of deer, oviduct and uterus, are also of endocrine origin.—Author's Abst.

The study of the internal secretion of the ovary. The properties of the follicular liquid. 1. Concentration, properties of the folliculine. Simonnet, S., Ann. de Physiol. 3: 586. 1927. Abst., Chem. Absts. 22: 449.

The preparation of the hormone is soluble in H<sub>2</sub>O and in lipid solvents. It contains no P or N, but only C, H and O. It is sensitive to oxidation agents, but resists the action of heat, especially in

acid or neutral media. The further study of its properties can only be undertaken after the isolation of the hormone in the pure state.

**The importance of the pituitary in the mechanism of development as activator of gonadal secretion (Die entwicklungsmechanische Bedeutung der Hypophysis als Aktivator der Keimdrüseninkretion).** Steinach, E. and H. Kun, *Med. Klin.* 14: 1928.

The first series of experiments was made on infantile rats, in order to find the causes for the late awakening of the testicular incretion (at the time of puberty). Water extracts of the anterior pituitary lobe prepared from cattle were used. Daily injections were administered, each corresponding to about one-quarter of the fresh anterior lobe substance. After 6 to 12 injections an extreme degree of somatic and psychic precocity in animals 38 to 45 days old was produced. Control animals reach puberty after 95 to 100 days. Further control experiments were made by interrupting the series of injections and demonstrating the consequent cessation of development. After resumption of the injections the development proceeded, which indicates that the observed phenomena are entirely due to the hormone of the anterior lobe. The authors conclude that the delay of the activating impulse from the anterior lobe is the cause for the delay of the testicular incretion and the natural maturity. The second series of experiments was made on eunuchoid male rats, in order to find out whether the role played by the anterior lobe on the endocrine mechanism is finished with the activation of the infantile testicle. The authors found that this is not the case and that the anterior lobe hormone also regulates gonadal incretion in the adult and thus protects the virility during life. The eunuchoid animals were brought to full maturity, as shown by the length and width of the seminal vesicles and the prostate, by spermatogenesis and by fully developed libido and potency. An interruption of the injections caused a relapse of the animals into the former state of eunuchoidism, and a resumption of the treatment brought them again to the height of virility. The ovary shows an analogous dependence. The last series of experiments was made on senile male rats to determine whether a fresh supply of anterior lobe hormone could revivify gonadal incretion. Typical senile rats, 19 to 24 months old, were used. After treatment the seminal vesicles and prostates were found to be considerably enlarged and filled with secretion, the musculature and intestinal tract were hyperemic and the psychic phenomena showed reactivation.—H. Benjamin.

**The biological action of the female sex-hormone (Ueber die biologischen Wirkungen des weiblichen Sexualhormons).** Steinach, E., M. Dohrn, W. Schoeller, W. Hohlweg and W. Faure, *Arch. f. d. ges. Physiol.* 219: 306-324. 1928.

Placental extract of cattle has now been concentrated by a technical process (details of which are not given) to the extent of 50,000

mouse-units per gram, from which preparation the active principle passes into solution to the extent of 500 units per cc. This solution is clear, free from protein, and resistant to acid, alkali, and boiling. It produces no harmful effect on males, even in strongest concentration. Injected into females, it causes marked hyperemia of the mammae through change of tonus in the peripheral vessels. The areola and mamilla of albino guinea-pigs are especially suitable for this test. The mammary apparatus of normal virgin females develops at the about the age of 17 weeks. This development takes place in infantile castrates after three weeks' treatment with the aqueous solution, and the age of 7 weeks. Since the hyperemia is visible after three days' treatment, this biological test can be used quantitatively. The mammary development is marked. Surface and vertical sections of the mammae show the typical close-packed lobules, separated by little fat and fibrous tissue, composed of large hyperplastic acini surrounded by high epithelium, the lumina filled with fat-rich secretion as in normal lactating glands. Secretion into the acini commences during the fourth week of treatment. Milk production, filling the ducts and sinuses, is recognizable after 7 to 8 weeks' treatment. The first period of milk-production lasts from 23 to 25 days, nearly as long as the lactation period of a primipara guinea-pig. The later period, produced through subsequent injections, lasts a shorter time. Complete appearances of hyperplasia and milk-secretion have been observed in females castrated at four weeks, when treatment commenced immediately after castration; in females also castrated at four weeks, when treatment only commenced two months later, and in males castrated at four weeks, who took on marked female characteristics. The uterus of the infantile castrates, especially the uterine mucous membrane, is markedly affected by the treatment, becoming hyperemic, with dilated blood vessels, and the whole organ increases in weight. The microscopic picture shows corresponding changes.—A. T. C.

**Follicular liquid and ovarian hormone.** Truffi, G., *Arch. di sc. biol.* 10: 787. 1927. *Abst., Chem. Absts.* 22: 456.

In experiments on the action of small doses of follicular liquid on females, the findings of other investigators were confirmed. Larger doses administered subcutaneously over a period of 20 to 40 days led to the prolongation of oestrus. In sexually developed animals, even though castrated, there appeared the typical genital phenomenon of post-oestrus which is normally observed on the presence of corpus luteum. In the immature animal sexual characteristics were also influenced. Follicular liquid may, therefore, replace the corpus luteum and interstitial glands. Follicular liquid had an "antitesticular" and "antimasculine" action on males. In the guinea pig there was a stoppage of spermatogenesis and a development of the mammary gland, and on the cock there was a change in the rate of

development of the comb. Follicular liquid produces the same genital modifications as are produced in the normal animal by the ovary. The liquid must, therefore, contain the specific ovarian hormone. The hormone shows a physiological and a sexual specificity, but not a species specificity.

**A hormone of heart movement. IX. Experiments with a heart-extract of warm blooded animals (Ueber ein Hormon der Herzbe-  
wegung. IX. Versuche mit einem Herzextrakt vom Warmblüter).  
Haberlandt, L., Arch. f. d. ges. Physiol. 219: 279-285. 1928.**

Similar results were obtained to those given by extracts from frogs' hearts.—A. T. C.

**The origin of the glucose in the hyperglycemia induced by pituitrin.  
Clark, G. A., J. Physiol. 64: 324. 1928.**

Studies were made on decerebrated, eviscerated cats whose blood sugar concentration was maintained constant by continuous glucose infusion throughout the experiment. Injection of 1 cc. pituitrin caused a fall in blood sugar within one hour. Simultaneous determination of hemoglobin showed that this was not due to blood dilution. Exclusion of the supra-renals from circulation did not alter the response. When pituitrin was followed by insulin injection, the blood sugar decrease by the latter was not retarded. With the liver excluded from circulation blood sugar concentration after insulin fell at about the same rate. It is concluded that the source of glucose in pituitrin hyperglycemia is the liver glycogen.—C. I. R.

**Effects of thymus, muscle and pituitary extracts on normal and  
thyro-parathyroidectomized dogs. Larson, E. and N. F. Fisher,  
Am. J. Physiol. 84: 330. 1928.**

Experiments were made on 31 dogs from which the thyroids and parathyroids were removed. It was found that extracts of calf thymus and muscle prepared by the same methods used in preparing potent parathyroid extracts have a slight ameliorative action on acute parathyroid tetany. These extracts, as well as pituitary extracts, do not cause sufficient changes in the calcium of the blood to account for their ameliorative action. No parathyroid-like principle could be demonstrated in the extracts as prepared.—R. G. H.

**Glandular elements in the posterior lobe of the human hypophysis.  
Lewis, D. and F. C. Lee, Bull. Johns Hopkins Hosp. 41: 241. 1927.**

Glandular tissue was found in the neural lobe of the human hypophysis cerebri at all ages. The authors studied complete serial sections of 30 human hypophyses and many other individual sections. Tubulo-racemose glands communicating with the hypophyseal cleft were seen frequently in the new-born and in children up to the fourth

year. After that time only occasional tubular glands were seen. The tubular glands were usually situated in the anterior and lateral portions of the posterior lobe, as well as the point of attachment of the hypophyseal stalk. In the gland cells was seen colloid material which stained like the substance found in the duct, cyst or cleft into which the gland emptied. The other chief glandular element was a basophilic cell which resembled the basophile of the anterior lobe in many particulars. This cell was present at all ages, but became more numerous, and invaded the posterior lobe progressively with increasing age. Masses of these basophilic cells were sometimes found high up along the hypophyseal stalk and near the dorsum sellae. Both varieties of these glandular elements were derived from the pars intermedia. The authors include a brief discussion of the relation of these glandular structures to each other and to the physiology of the posterior lobe.—W. J. A.

The presence of pituitrin in the ventricular cerebro-spinal fluid and its absence in the lumbar cerebro-spinal fluid (*Présence d'hypophysine dans le liquide céphalorachidien ventriculaire et dans les liquides de ponction occipitale; son absence dans les liquides de ponction lombaire*). Mestrezat, W. and V. Cauiaert, *Arch. internat. de physiol.* 28: 1. 1927.

The presence of the pituitary principle was determined by the action on the isolated uterus of the virgin guinea pig. Ventricular cerebro-spinal fluid was withdrawn from both dogs and horses by puncture between the occiput and the first cervical vertebra. Though the liquid removed by occipital puncture was active, the liquid withdrawn by lumbar puncture was pharmacologically inactive. From their results these investigators feel that, though the hypophysis is usually considered to be a gland of internal secretion, it is of a special type because the blood and lymph vessels absorb the pituitrin after it has been secreted into the cerebro-spinal fluid.—E. L.

Metabolic tests in *dystrophia adiposo-genitalis*. Nonnenbruch, W., *Deutsches Arch. f. klin. Med.* 156: 312. 1927.

Nonnenbruch, in his article on metabolic tests in *dystrophia adiposo-genitalis*, cites a case of *dystrophia adiposo-genitalis* and hypophyseal tumor with lowered basal exchange. A pronounced rise in metabolic exchange took place after a meat diet, the maximum occurring after the 4th hour, and not after the 2nd hour, of food assimilation, as claimed by Kestner, Plaut and Schadow, who deem a single analysis after two hours sufficient for the test. He agrees with Durr, Lubin et al. that a series of analyses are necessary for several hours after a meat diet. Furthermore, he indicates that in the case under discussion the specific-dynamic albumin action does not depend upon the anterior pituitary lobe and calls for a series of analyses after a meat diet to estimate the increase of metabolic ex-



change. He again disputes Kestner's theory. The latter considers the lowering of the metabolic exchange by meat diet as important in differential diagnosis between thyrogenous and hypophyseal obesity. Weight is given to the opinion that centers of the midbrain which influence metabolism are in turn influenced by the hypophysis. Biedl differentiates between a pure cerebral form of Fröhlich type and a pure hypophyseal form of Fröhlich syndrome. There are a number of cases in literature which show an inconstancy in the basal exchange. The lowering of the basal exchange is not necessarily a part of the dystrophia adiposo-genitalis syndrome. The basis for this lowering of exchange is not definitely known. The thyroid may play a part, as in endocrine disturbances several glands are involved.

—H. G. Beck.

**Sex-determining action of the anterior pituitary on males (*Geschlechtssprügende Wirkungen des Hypophysenvorderlappens am Männchen*).** Voss, H. E. and S. Loewe, *Arch. f. d. ges. Physiol.* **218**: 604-609. 1928.

A single implantation of less than 0.02 grams of anterior pituitary gland of the sheep suffices to bring a pre-puberal male mouse to puberty. The stimulating action is only on the testis, the growth of the remainder of the genital tract following secondarily to the accelerated ripening of the testis.—A. T. C.

**Growth response to anterior hypophyseal extract by the castrated male rat.** van Wagenen, Gertrude, *Am. J. Physiol.* **84**: 468. 1928.

In controlled experiments on 10 castrated rats, it was found that the growth response to anterior pituitary extract was retained.

—R. G. H.

**Influence of epinephrine on the carbohydrate metabolism of fasting rats.** Cori, C. F. and Gerty T. Cori, *Proc. Soc. Exper. Biol. & Med.* **25**: 358-361. 1928.

When epinephrine (0.02 mgm. per 100 gm.) was injected subcutaneously into 24-hour fasting rats, the liver glycogen showed a marked increase, whereas the glycogen stores in the rest of the body decreased on an average a little more than the liver glycogen increased. Determinations of the gaseous metabolism revealed that the R. Q. remained at the fasting level (0.715) after the epinephrine injection, whereas the caloric output increased. It is assumed that epinephrine mobilizes muscle glycogen. The lactic acid thus produced enters the blood stream, is carried to the liver and there deposited as glycogen. This explanation is supported by the observation that d-lactic acid, given by mouth, forms glycogen in the liver of rats.—G. T. Cori.

**The insulin requirements on various diets.** Blatherwick, N. R., W. D. Sansum, Marion Bell and Elsie Hill, *J. Metab. Research*, 7-8: 39. 1925-1926.

A man, 57 years of age, having a very severe case of diabetes, was the experimental subject. The plan of the experiment was to keep the protein and calories constant and to vary the carbohydrate content of the diet. The basal diet contained 281 grams carbohydrate, 72 grams protein, 71 grams fat, and a total of 2,051 calories. In three periods on this diet, 143, 151, and 148 units of insulin were required to keep the urine free from gross sugar. When the carbohydrate of the diet was raised from 281 to 412 grams the insulin requirement was only increased to 166 units. The results show that the insulin requirement is not entirely governed by the potential glucose of the food. The requirement for insulin is dependent upon all of the foodstuffs comprising the diet.—Authors' Abst.

**The secretion of pancreatic juice—a glycolytic factor in blood** (*Die Sekretion des Pankreassaftes—ein glykolytischer Faktor im Blute*). Boldyreff, E. B., *Arch. f. d. ges. Physiol.* 218: 553-567. 1928.

The sugar content of normal fasting animal's blood shows periodic variations. It is lower during pancreas secretion than in intervals between this secretion. In absence or inhibition of pancreas secretion, or during removal of the secretion by fistula, the blood sugar is increased. The pancreatic secretion absorbed into the circulation from the small intestine is considered to be one of the chief factors in changing the value of the blood sugar. Blood sugar is higher during active stomach secretion than when the reaction of the stomach is alkaline. Pancreatic juice contains a glycolytic enzyme.  
—A. T. C.

**The formation of sugar from fatty acids in the depancreatized dog injected with epinephrine.** Chaikoff, I. L. and J. J. Weber, *J. Biol. Chem.* 76: 813. 1928.

Repeated injections of epinephrine into depancreatized dogs on the third and fourth days after the withdrawal of insulin and food, caused a glycosuria greatly in excess of the amount that could be accounted for as being derived from the glycogen of the liver, from protein and from glycerol. The authors conclude that the extra sugar was derived from fatty acids.—M. O. L.

**The influence of the vagus on the islets of Langerhans. III. Further experiments on vagotomy.** Clark, G. H., *J. Physiol.* 64: 229. 1927.

Section of the right vagus in cats produced an immediate fall in blood sugar concentration. This is not due to stimulation in the act of cutting, to interfere with pulmonary cardiac function nor to cutting off of impulses to the liver or adrenals. It is suggested that the

effect is due to cutting off inhibitory impulses controlling insulin secretion.—C. I. R.

**Relations between the internal and external secretions of the pancreas** (*Relations entre la sécrétion interne et la sécrétion externe du pancréas*). Coelho, E. V. and J. C. Oliveira, *Compt. rend. Soc. de biol.* 98: 477. 1928.

In fourteen out of twenty human cases it was shown that an augmentation of the external secretion of the pancreas was accompanied by an increase in insulin output.—J. C. D.

**The influence on glucose solutions of insulin and of muscle from a normal and a diabetic dog** (*Action in vitro de l'insuline et des muscles de chiens normaux et diabétiques sur le glucose*). Combes, T. J. C., *Compt. rend. Soc. de biol.* 98: 174. 1928.

Normal muscle and insulin destroy in time the rotating power of glucose solutions. Muscle from diabetic dogs influences the rotating power very little.—J. C. D.

**Studies on crystalline insulin. III. Further observations on the crystallization of insulin and on the nature of the sulphur linkage. The isolation of cystine and tyrosine from hydrolized crystalline insulin.** De Vigneaud, V., H. Jensen and O. Wintersteiner, *J. Pharmacol. Exper. Therap.* 32: 367. 1928. **IV. The isolation of arginine, histidine and leucine.** *Ibid.* 387. **V. The distribution of nitrogen in crystalline insulin.** *Ibid.* 397.

Detailed precautions are given for the preparation of crystalline insulin. Hydrolysis of crystalline insulin gave 15.6 per cent total nitrogen, 12.2 per cent of tyrosine, and 14.2 per cent cystine combined in the form of a dipeptide, 7.6 per cent free cystine. Both cystine and tyrosine are present in the insulin molecule. The presence of arginine, histidine and leucine has also been proven and that of lysine is indicated. The nitrogen distribution in the insulin molecule is reported in detail.—C. I. R.

**Insulin and hypercholesterolemia** (*L'insuline et l'hypercholestérolémie*). Fellegi, G., *Ann. de med.* 22: 330-344. 1927.

After a review and discussion of the literature with a good bibliography, the author gives the following résumé: Insulin lowers the blood cholesterol if it is elevated, by stimulating the hepatic cells eliminating cholesterol. Insulin also fixes the cholesterol in the fat of the tissues, inhibits cholesterol production by the adrenals and excites the destructive function of the organs responsible for its destruction. Fellegi believes that insulin treatment is indicated, not only in diabetes, but in cholelithiasis, cholecystitis and in icterus due to gall stones.—E. L.

Regulation of glycemia in diabetic dogs by transplantation of varying amounts of pancreas (*La régulation de la glycémie des chiens diabétiques par des quantités variées de tissu pancréatique transplanté*). Gayet, R. and M. Guillaumie, *Compt. rend. Soc. de biol.* 98: 584-586. 1928.

Transplanted pancreas without nervous connections brings blood sugar back to normal within a period of a few hours. The larger the graft the more rapid the return to normal.—J. C. D.

Effect of insulin on the blood sugar in nephrectomized dogs (*Influence de l'insuline sur le taux du sucre sanguin chez les animaux nephrectomisés*). Gnoinski, H., *Compt. rend. Soc. de biol.* 98: 785-786. 1928.

Insulin reduces the blood sugar as in normal dogs, but its effects are much prolonged —J. C. D.

Is there a substance producing hyperglycemia in the blood of diabetics (*Existe-t-il dans le sang diabétique une substance à action hyperglycémique*)? Hédon, E., *Compt. rend. Soc. de biol.* 98: 564-567. 1928.

Blood from a depancreatized dog was treated according to Loewi's technic, i. e. dialyzed and extracted with alcohol. This extract failed to show, as claimed by Loewi, any hyperglycemic action.  
—J. C. D.

Basal metabolism in experimental pancreatic diabetes (*Le quotient respiratoire et le métabolisme de base dans le diabète pancréatique expérimental*). Hédon, L., *Arch. Internat. de physiol.* 29: 175-212. 1927.

Eleven dogs were used. In the 15 tables included in the paper the CO<sub>2</sub> exhaled, O<sub>2</sub> consumed, urea and sugar excretion, and heat production are given for the normal animal, after making a pancreatic graft and after removal of the graft. The results show that there is an augmentation of the basal metabolic rate after pancreatectomy. This effect is not due to the trauma of the operation, nor to the removal of the external secretion of the pancreas. This increase becomes greater during the survival period of the animal and usually there is a 30 per cent increase. The cause of this elevation is obscure, but it may be due to increased sugar formation from the proteins —E. L.

Mechanism of the action of synthalin. Hetenyi, G., *Klin. Wehnschr.* 6: 2288. 1927. *Abst., Chem. Absts.* 22: 814. 1928.

During the hypoglucemic crisis following an injection of insulin, the glucose concentration in the blood and tissues is markedly reduced; but the total carbohydrate content of the liver is increased.

The author believes that the crisis is brought on by the action of the liver cells. Synthalin, unlike insulin, reduces the carbohydrate content of all of the tissues, including the liver, and a hypoglycemic crisis is not obtained after administration of synthalin.

A study of 22,800 blood sugar estimations—fasting and postprandial—in non-diabetic individuals. John, H. J., *Ann. Int. Med.* 1: 470-481. 1928.

The author in the analysis of his data found that 14.14 per cent of the blood sugars were below 80 mgm. per 100 cc. of blood; 7.85 per cent were below 75 mgm., and the lowest value was 30 mgm. This indicates that low blood sugars are not of infrequent occurrence in the normal human being, as none of these patients had registered any complaints. John believes that there should be no alarm when exogenous insulin lowers the blood sugar below 60-65 mgm. because the endogenous insulin apparently does the same.

—E. L.

Ideals in the treatment of diabetes and methods for their realization.

Joslin, E. P., *New England J. of Med.* 198: 379. 1928.

The effectiveness of the treatment of diabetes is shown in certain striking cases. What can be done for these can be done for most diabetics. High fat diets should be avoided, as they favor arterio-sclerosis and premature old age. Careful diet helped with small amounts of insulin is the best treatment. A camp for diabetic youngsters, where they can enjoy out-of-door sports has proved very successful.—J. C. D.

The hyperglycemic effect of blood from depancreatized dogs (*Action hyperglycémisante du sang des chien dépancraté*). Képinov, L. and S. Petit-Dutaillis, *Compt. rend. Soc. de biol.* 98: 425. 1928.

If blood from a diabetic dog is injected into a normal dog, the blood sugar rises sharply, sinks to almost normal, and then rises again. If glucose or blood from normal dogs just after a glucose injection is used, there is a rise in blood sugar, followed by prolonged hypoglycemia. The assumption is made that in diabetic blood there is a substance "glycimine," which opposes the fixation of glucose by the cells.—J. C. D.

The sugar content of whole blood of different vessels and its partition between plasma and corpuscles under normal conditions and after insulin and adrenin administration to angiostomised dogs (*Vollblutzucker-gehalt verschiedener Gefäßgebiete und seine Verteilung auf Plasma und Formelemente unter normalen Verhältnissen und bei Insulin—und Adrenalineinverleibung nach Versuchen an angiostomierten Hunden*). Kotschneff, Nina, *Arch. f. d. ges. Physiol.* 219: 407-410. 1928.

Insulin hypoglycemia is produced through decreased liver sugar-production and relatively increased sugar output to the organs. Adrenin hyperglycemia is brought about especially by increased mobilization from the liver. During absorption from the intestine relatively more sugar is taken up by the corpuscles than during sugar-mobilization from the liver, during fasting or after adrenin injection, and also in hypoglycemia following insulin. During fasting muscles draw equally from plasma and corpuscles, spleen draws from neither, while other organs draw more from plasma than from corpuscles. Under insulin action, the organ tissues not only do not derive sugar from the red cells, but part of the plasma-sugar passes into the corpuscles.—A. T. C.

On the increase in insulin following injection of posterior lobe extract (*Sur les causes de l'hyperinsulinémie consécutive à l'injection d'extrait hypophysaire postérieur*). LaBarre, J., *Compt. rend. Soc. de biol.* 98: 330. 1928.

Experiments were tried on dogs first, with a circulatory anastomosis between two animals, and then with a depancreatized, decapsulated animal into whose carotid-jugular circulation a pancreas was introduced. These showed that posterior pituitary lobe extract increases the insulin in the blood by direct action on the islet tissue, not through vagal action.—J. C. D.

Evidence concerning the effect of insulin on carbohydrate tolerance. LeFevre, W. M., *Ann. Int. Med.* 1: 607-612. 1928.

Of the 57 cases of diabetes reported by this author, about half of them required insulin when kept on a Petty diet. Of the patients requiring insulin, 50 per cent were able to cease their injections in two weeks to fourteen months. Some of the cases which still continued insulin were complicated by other conditions. From his results, the author concludes that adult diabetics may improve their tolerance for carbohydrate so that insulin may not be required.

—E. L.

Action of the salts of nickel and cobalt on insulin hyperglycemia (*Action des sels de nickel et de cobalt sur l'hypoglycémie insulinaire*). Magenta, M. A., *Compt. rend. Soc. de biol.* 98: 169. 1928.

These salts have no appreciable action.—J. C. D.

Regulations of the blood sugar and water concentrations (*Blut-zuckerregulation und Wasserhaushalt*). Marx, H., *Klin. Wchnschr.* 6: 1750. 1927. *Abst., Chem Absts.* 22: 624.

A close relationship exists between the blood sugar and water concentrations in the blood. Sugar overeating leads to hyperglycemia and hydremia. Ingestion of water gives a blood dilution curve

that parallels the sugar hyperglucemia curve very closely. The magnitude of the dilution changes induced by ingesting either water or sugar is very largely independent of the absolute quantity of these substances ingested. Repeated ingestion of water or sugar leads to a refractory period. Injection of insulin leads to a hypoglucemia and to a thickening of the blood.

The insulin neutralizing power of the blood of diabetics and non-diabetics (*Sur le pouvoir de neutralisation du sang de sujets diabétiques et non diabétiques vis-a-vis de l'insuline*). The neutralizing power of the blood for insulin lies in the corpuscles (*Le pouvoir de neutralisation du sang vis-a-vis de l'insuline est d'origine globulaire*). The neutralization of insulin by the blood is due to an intracorpuseular substance (*La neutralisation de l'insuline par les globules sanguins est due a une substance anti-insuline intraglobulaire*). Mauriac, P. and E. Aubertin, *Compt. rend. Soc. de biol.* 98: 233. 1928.

Defibrinated blood from normals and from diabetics was mixed with insulin. After incubation these solutions were tested for the activity of the insulin by injection into rabbits. In the blood of certain diabetics resistant to insulin treatment, a rapid neutralization of insulin took place. Centrifuging citrated blood proved that this neutralizing power was in the cells. By laking the cells it was shown that this was not dependent on their integrity, but was due to an insulin neutralizing substance present in them.—J. C. D.

The effect of successive doses of insulin on the animal body. Ohara, Y., *J. Biophysics* 2: 39. 1927. *Abst., Chem. Absts.* 22: 266.

After daily injections of convulsive doses of insulin in rabbits, there was an increase in body weight, although convulsions often occurred. A hypertrophy of the cortex of the adrenals was found.

A case of diabetes mellitus that became one of atypical renal glycosuria. Mason, E. H., *Canad. M. A. J.* 18: 557-560. 1928.

A woman, aged 68, showed, on admission to hospital, diabetes mellitus, chronic nephritis, chronic myocarditis, hypertension, arteriosclerosis, passive congestion of the lungs and liver, umbilical hernia, and cataract (left). She was balanced with insulin, discharged, and followed through the outdoor department for two months, during which time she was free from glycosuria. Marked failure of compensation appeared, confining her to bed, her appetite failed, and she stopped insulin. She was re-admitted to the hospital eight months after discharge, and again showed glycosuria, but without hyperglycaemia, and gave a typical sugar tolerance curve for renal glycosuria. After 40 days in the hospital (without insulin and with unrestricted carbohydrate) she was discharged, and was admitted 19 days later acutely ill from failure of compensation,

dying 3 hours later. Autopsy showed numerous large islets of Langerhans in the pancreas. The initial diagnosis of diabetes mellitus was based upon a fasting bloodsugar of 0.26 per cent, with glycosuria, and, after control of diet, a moderate fasting hyperglycaemia reacting to insulin, and no glycosuria.—A. T. C.

**Treatment of diabetes with an acid-alcohol extract of plants rich in vitamin B.** Mills, C. A., *Am. J. M. Sc.* 175: 376-383. 1928.

From his clinical experience Mills found that vitamin B stimulated the appetite and growth in children, so extracts of vitamin B rich food were prepared. Alfalfa, sweet clover, corn silk, onions, carrots, etc., were treated with 40 per cent ethyl alcohol containing 0.4 per cent HCl. No heat was used during the process. After extraction, the HCl was neutralized with NaOH and the precipitate removed by filtration. In some cases the alcohol was removed by evaporation. Of the seven cases presented five show that vitamin B decreases the sugar excretion in diabetes. One of the cases was complicated by renal glycosuria and another of the patients left the hospital when the effects were beginning to be definite. The advantage of this extract is that it is effective when given orally.

—E. L.

**The insulin-glucose treatment of traumatic shock.** Padgett, E. C. and T. G. Orr, *Surg. Gynec. Obst.* 46: 783-788. 1928.

The authors consider, from experimental evidence, that probably no better results are obtained by this treatment than by hypertonic glucose or sodium chloride intravenous injections.—A. T. C.

**Atrophy of subcutaneous fat following insulin injections.** Rabino-witch, I. M., *Canad. M. A. J.* 18: 560-561. 1928.

Eight such cases are recorded. In only two were the areas of atrophy of any considerable size. The condition appears to bear no relation to progress. No trace of lipase could be detected in a large amount of insulin preparation similar to that used by these patients.

—A. T. C.

**Action of insulin on experimental anaemia in the rabbit. Notes on inhibitory substances in the blood during hyperglycemia (Action de l'insuline sur l'anémie expérimentale du Lapin. Contribution à l'étude des substances inhibitrices du sang, dans l'hyperglycémie).** Rentz, E., *Compt. rend. Soc. de biol.* 98: 816-818. 1928.

Anemia produced a hyperglycemia. Insulin has less influence on the blood sugar in these cases than in normal animals—J. C. D.

**The action of myrtillin in pancreatic insufficiency.** Shpiner, L. B., *Am. J. Physiol.* 84: 396-400. 1928.



On the basis of experiments on 2 animals it was concluded that myrtillin reduces the hyperglycemia and the glycosuria of a totally depancreatized dog (as reported by Wagner and Allen), stabilizing, so to speak, the blood sugar which would otherwise have a tendency to fluctuate within rather wide limits. After the loss of 19/20 of the pancreas, the feeding of myrtillin prevented the development of hyperglycemia and glycosuria. The mild hyperglycemia and glycosuria which followed the administration of desiccated thyroid extract to dogs from which  $\frac{7}{8}$  of the pancreas had been removed, were eliminated by the administration of myrtillin.—R. G. H.

The action of synthalin on the organism (*Über die Wirkung des Synthalins im Tierorganismus*). Simola, P. E., *Ztschr. f. physiol. Chemie*, 168: 274. 1927. *Abst., Physiol. Absts.* 12: 564.

The lowering of blood sugar after synthalin injection is not so clear and characteristic as with insulin. The lowering is sometimes slight and long delayed, and is in some cases preceded by a marked rise. In some experiments a considerable rise only was observed. When the blood sugar fell, a decrease in the inorganic phosphate was found; in the cases of a rise in blood sugar, the inorganic phosphate also rose. The symptoms of synthalin poisoning resemble those of guanidine poisoning.

Insulin-like substances in higher plants and microorganisms. Simola, P. E., *Ann. Acad. Sci. Fennicae* 29: 1927. *Abst., Chem Absts.* 22: 1928.

There occurs in plants and bacteria certain substances which can reduce blood sugar considerably. These insulin-like substances are best extracted from the plant material with acid-alcohol or rubbing up the material with picric acid and extracting with acetone. Such substances have been isolated from potatoes, oats hulls, yeast, rhubarb leaves and living and dead bacteria. It was noted in the intravenous and subcutaneous injection of these substances into rabbits that the lowering of the blood sugar (40 per cent in one case) was greatest after 2 hours. One case showed a 4-hour maximum. Actual hypoglycemia convulsions were not observed. Toxic symptoms were produced in rabbits, if the insulin-like substance was not thoroughly purified. On account of the small amount of the pure material available, the chemical nature of these substances could not be determined. Possibly they are guanidine derivatives.

Inflammation involving the islands of Langerhans in diabetes. Stansfield, O. H. and W. Shields, *New England J. Med.* 199: 686-687. 1928.

A report is given of the autopsy findings in two girls, one six and one seven years old, who died after acute diabetes.—J. C. D.

The inactivity of insulin injected directly into the intestine and experiments to ascertain the cause of the inactivity (*Über die Unwirksamkeit des direkt in den Darm eingeführten Insulins und Versuche zu deren Erklärung*). Stasiak, A., *Biochem. Ztschr.* 188: 24. 1927.

The work reported was undertaken to ascertain, if possible, why insulin given by mouth has practically no effect on blood sugar. Rabbits were used and the insulin or the control solutions were introduced directly into the intestine through an abdominal window. Eight different series of experiments were carried out, and each series was made up of from 6 to 8 animals. The results reported indicate that insulin dosage of 40 to 80 international units in N/100 HCl directly introduced into the intestine has no blood sugar lowering action; in fact, the blood sugar was in most cases raised. Control experiments with N/100 HCl alone, introduced under the same conditions, gave increased blood sugar, while 9 per cent NaCl was without effect. Rabbits injected with the contents of ligated loops of intestine of rabbits which had been given insulin, 2 to 4 hours previously, again showed no hypoglycemia. Insulin apparently is destroyed or adsorbed by intestinal cells. It was found that insulin incubated with ground intestine at 37 degrees for three hours, with constant shaking, lost its activity. However, if the mixture was not agitated and the insulin was in contact with the intestinal mash for only a short time, it apparently was neither destroyed nor held in a firm union. It could be reactivated quantitatively by alcohol treatment. Intestinal cells previously destroyed by treatment with NaF no longer had the power to inactivate insulin. The last series reported that occasionally a substance can be isolated from the intestine which has insulin-like action. Hypoglycemia and convulsions were produced in starved rabbits injected with a mash of rabbit intestine similar to the insulin experiment, but where insulin was not used.—Estelle Hawley.

**Insulin and blood pressure.** Strisower, R., *Wien. Arch. f. inn. Med.* 14: 429. 1927. *Abst., Chem Absts.* 22: 1191. 1928.

A fall in blood pressure and in blood sugar was noted after the injection of insulin in cases of hypertension with diabetes, essential hypertension and hypertension with nephritis. The fall in blood pressure and also in blood sugar was most marked in the diabetics with hypertension, but the fall in blood pressure and in blood sugar did not run parallel. Probably the hormone of the pancreas has a central action analogous to that of pituitrin and of the hormones of other glands of internal secretion, such as the thyroid gland and the hypophysis. The explanation of the fall in blood pressure after insulin is only a part of the problem of hypertension in general.

**Insulin and the diabetic pancreas.** Susman, W., *Edinburgh M. J.* 35: 206. 1928.

This is a study of the islet tissue from thirteen diabetics who had had insulin treatment. Eleven died of coma and two of causes independent of the diabetes. There was more hyperplasia than is found in the islets of untreated diabetics, but evidence of permanent repair was lacking.—J. C. D.

**Diabetic coma and insulin (Koma diabeticum und Insulin).** Weiss, T., *Deutsches Arch. f. klin. Med.* 156: 226. 1927.

A statistical study of the cases of diabetic coma treated in the Dresden-Johannstadt City Hospital from 1910 to 1927 shows that before the use of insulin all patients who entered in a comatose or precomatose condition died; since insulin has been used—a period of about three and a half years—all patients entering in a precomatose condition (15) have recovered, while of the 23 who were in a state of fully developed coma, six have recovered and 17 have died. The seeming discrepancy between the author's results and those of other observers, for instance, of Umber, is explained by the fact that the latter does not distinguish between coma and a precomatose state. Doses of 100-150 units of insulin in the first 24 hours seemed to be more effective than extremely high doses, although no ill effects have been observed from the latter. Intravenous injections of calorse, given usually after the blood sugar has begun to fall, were very effective, but alkali infusions were entirely without effect. In most of the cases of coma in which death occurred, if the patients were not actually moribund upon entrance, the carbohydrate metabolism was controlled by the insulin and death resulted, not from the coma, but from increasing weakness of the heart. In three cases, however, the relapse which followed did not resemble the usual picture of heart failure, but rather that of uremia. The clinical symptoms—increased residual nitrogen, an increased blood pressure after a transient anuria, albumen and clindroids in the urine, the simultaneous appearance of coma and of motor disturbances, all speak for this interpretation, in spite of the fact that at autopsy the kidneys showed almost no pathological changes. The author feels that death probably resulted in these cases from a functional damaging of the kidneys occurring before and during the coma, which was of such severity that the kidneys were unable to recuperate as usual. The picture in these cases therefore parallels that in the cases of heart failure, in which also the anatomical findings do not show sufficient damage to account for death.—H. J. J.

**Regulation of metabolism. X. Glycogen in fatty tissue and the possibility of change of fat into carbohydrate (Stoffwechselregulationen. X. Ueber Glykogen im Fettgewebe und über die Möglichkeit der Umwandlung von Fett in Kohlehydrat).** Wertheimer, E., *Arch. f. d. ges. Physiol.* 219: 190-201. 1928.

After prolonged hunger, followed by food, glycogen (up to 2 per cent) is invariably found in the fatty tissues of rats. In Octo-

ber and November glycogen is invariably found in the fat-bodies of *Rana esculenta*, which remains there during hunger and after strychnine poisoning. The results are considered to support the change of fat to carbohydrate.—A. T. C.

The treatment of parathyroidectomized dogs with cod liver oil. Brougher, J. C., *Am. J. Physiol.* **84**: 583. 1928.

A controlled study was made on 18 dogs. It was found that addition of cod liver oil to a mixed stock diet for thyro-parathyroidectomized dogs delayed the onset of tetany and lessened its severity when it did occur. Serum calcium in control and in test animals dropped to the tetanic level, but tended to approximate the normal in 30 to 40 days in the animals given cod liver oil. The point is further confirmed that low serum calcium is not always accompanied by tetany. Cod liver oil relieves tetany and benefits parathyroidectomized dogs either by improving calcium absorption, mobilizing body calcium, or increasing the ratio of ionized to un-ionized calcium. Thyro-parathyroidectomized animals have been carried through estrus, pregnancy and lactation by the addition of cod liver oil to the stock diet.—Author's Abst.

Experimental obstructive jaundice. II. Modification of the parathyroid tetany mechanism in jaundice. Buchbinder, W. C. and Ruth Kern, *Arch. Int. Med.* **41**: 754-763. 1928.

There is a marked diminution generally or an absence of tetany following thyroparathyroidectomy on jaundiced adult dogs and puppies. The survival period after thyroparathyroidectomy is prolonged especially for animals that have been jaundiced for some time. The acutely jaundiced dog is more susceptible to a severe and terminal tetany. Indirect evidence is presented of a functionally or structurally altered mechanism of tetany in obstructive jaundice. This is threefold and is based on: (a) the response of the thyroparathyroidectomized animal; (b) the relief of tetany by the intravenous injection of bile, and (c) the absence of tetany in late obstructive jaundice in puppies in which the blood serum calcium may reach the tetany level.—Authors' Abst.

Calcium content of maternal and foetal blood serum following injection of parathyroid extract in foetuses in utero. Hoskins, F. M. and F. F. Snyder, *Proc. Soc. Exper. Biol. & Med.* **25**: 264. 1928.

In these experiments in which parathyroid extract (Collip) was injected into foetuses in the dog, there was no evidence that the active substance reached the maternal circulation, as indicated by the calcium content of the maternal blood serum. The foetal blood serum obtained at the end of each experiment was found in the non-injected foetuses to be about 1 to 3 mgm. higher in calcium than

the maternal serum. In foetuses which had been injected previously with parathyroid substance, the calcium content of the serum was more than 3 mgm. higher than in the maternal serum. These findings in the case of parathyroid extract are in agreement with previous observations which have been made upon the effect on the mother of the injection of insulin, adrenalin, and pituitrin in rabbit and guinea pig foetuses, in utero. No evidence has been obtained that these endocrine substances pass from foetus to mother across the placental boundary.—M. O. L.

**Parathyroid extract as a factor in ossification and growth.** Ortega, F. E., *Progresos de la clínica* 35: 836. 1927. Abst., J. A. M. A. 90: 653.

Experiments on dogs and clinical tests in three little girls demonstrated that the parathyroid hormone is apparently an important agent in bone and body growth. This is the treatment of choice in any case of retarded growth in which thyroid medication has brought the basal metabolism to normal, but has left the growth disturbance uncorrected. Doses of parathyroid extract should be very small and should be associated with oral administration of calcium lactate.

**The effect of parathyroid extract on mineral metabolism in infantile tetany.** Shohl, A. T., A. M. Wakeman and E. Y. Shorr, *Am. J. Dis. Child.* 35: 392-397. 1928.

Small amounts of parathyroid extract were administered to two patients with infantile tetany. It had little effect on one child, while in the second it controlled the symptoms and showed an improvement as measured by clinical and chemical results. The improvement was transitory and ceased when treatment was discontinued. The alteration in the chemical picture was brought about without gross change in either calcium or phosphorus metabolism. During the period of administration of the parathyroid extract (with relief of symptoms) there was a normal excretion of sodium and potassium. During the relapse following withdrawal of the extract, the excretion of sodium was increased and potassium was retained.—M. B. G.

**Tetany and chronic diarrhea.** Snell, A. M. and H. C. Habein, *Ann. Int. Med.* 1: 694-706. 1928.

A case of tetany in which diarrhea was the undoubted cause is reported. The tetany was controlled by the administration of parathormone and calcium lactate. A discussion of the relation of tetany to the gastro-intestinal tract is included.—E. L.

**Influence of thyroidectomy on the absorption of water by the tissues** (*Action de la thyroïdectomie sur l'hydrophilie tissulaire*). Bernardbeig, J. and M. Sendrail, *Compt. rend. Soc. de biol.* 98: 578-580. 1928.

Thyroidectomized rabbits were tested for the rate of water absorption by subcutaneous injections in the lobe of the ear. In three out of five which showed typical symptoms of hypothyroidism, absorption was more rapid.—J. C. D.

**Hyperthyroidism caused by pyelitis.** Bonilla, E. and J. F. Velasco, *Med. ibera* 1: 201. 1928. *Abst., J. A. M. A.* 90: 1672.

In a girl, aged 23, a typical hyperthyroid syndrome—goiter, tremor, tachycardia, loss of weight—followed pyelitis of calculous origin. The condition subsided completely after the pyelitis was cured. Previous antithyroid treatment had failed.

**Creatine excretion in artificial hyperthyroidism.** Carson, D. A., *Proc. Soc. Exper. Biol. & Med.* 25: 382. 1928.

Following a recent report on the excretion of creatine in hyperthyroidism and the effect of iodine therapy upon this condition, an attempt was made to produce creatinuria experimentally by the administration of thyroid extract. Three subjects were used, two of whom were in good health, and one an elderly man suffering from arteriosclerosis. Large amounts of thyroid extract were required to elevate the basal metabolism and produce creatinuria and the excretion was irregular except in the case of the arteriosclerotic individual. His excretion reached a maximum of 483 mgm. The effect of iodine in his case could not be determined.—Author's Abst.

**Stammering produced by thyroid medication.** Gordon, M. B., *Am. J. M. Sc.* 175: 360. 1928.

The untoward symptoms produced by thyroid medication are essentially those of an acute thyroiditis and are generally disturbances of the central nervous, gastro-intestinal and cardiovascular systems. Stammering may be produced by thyroid extract and should be considered as a manifestation of a general nervous excitation following disturbance of the central nervous system. When observed during the course of thyroid treatment it should be treated as any other toxic symptom by an immediate suspension of the medication. The administration of the thyroid should not be resumed until some time has elapsed after the disappearance of the stammering and then only with small doses. Five cases of childhood myxedema and hypothyroidism are reported in which stammering occurred during the course of thyroid treatment. The relationship between the stammering and the medication is clearly apparent.—Author's Abst.

**Histological study of the thyroid of the guinea pig in experimental scurvy.** Harris, Katharine D. and Erma A. Smith, *Am. J. Physiol.* 84: 599. 1928.

As a result, of scurvy (8 cases) the thyroid gland of guinea pigs showed an increased amount of interfollicular cells, a decrease in colloid, an increase in the number of vacuoles, and a lengthening of the cells lining the follicles, the degree of change depending on the length of time the animals survived the scurvy-producing diet. Acute starvation of guinea pigs (2 cases) revealed no changes in the thyroid. The results are interpreted as an indication of involvement of the thyroid as a consequence of vitamin C deficiency.

—R. G. H.

Cataract and postoperative tetany. Jaques, L., *Am. J. M. Sc.* **175**: 185. 1928.

A good review of cataract formation after thyroidectomy is given by the author, with a history of two cases. Neither of these developed severe tetany, because of being controlled by parathormone medication. The author stresses the point that the postoperative tetany should be promptly controlled, so as to avoid lenticular opacities.—E. L.

Action of thyroxin on the autonomic nervous system (*Action de la thyroxine sur l'innervation autonome*). Kalnins, V., *Compt. rend. Soc. de biol.* **98**: 800-802. 1928.

Thyroxin re-enforces the effects of adrenin on the rabbit's intestine and uterus. It seems to increase the excitability of the sympathetic end organs but only in massive doses. In small doses it increases para-sympathetic excitability in the intestine but in large doses paralyzes it.—J. C. D.

The effect of thyroxin on the autonomic excitability of the heart (*Action de la thyroxine sur l'excitabilité autonome du coeur*). Kalnins, V., *Compt. rend. Soc. de biol.* **98**: 802-804. 1928.

No influence of thyroxin on the frog's heart could be noted.

—J. C. D.

The influence of the thyroid on the distribution of iodine, sugar and amino acids in the blood (*Ueber der Einfluss der Schilddrüse auf die Verteilung von Jod, Glucose und Aminosäuren im Blut*). Kraft, R., *Mittz. Grenzgeb. Med. u. Chir.* **40**: 433. 1927. *Abst., Chem. Absts.* **22**: 450.

The distribution of the iodide between plasma and the corpuscles is approximately the same where different coagulants are used. It is independent of the amount of iodide and is about the same for different animals of the same species. It is influenced by the proportions of blood cells to plasma. The relationship is not changed by hyperthyroidism or thyroidectomy, but is changed after intravenous injections corresponding with the escape to the tissues.

The distribution of glycine and glucose on the plasma and the corpuscles is the same in normal, hyperthyroid and thyroidectomized animals.

**Studies on vigor. XV. The effect of thyroidectomy on spontaneous activity in the rat, with a consideration of the relations of the basal metabolism to spontaneous activity.** Lee, M. O. and E. F. Van Buskirk, *Am. J. Physiol.* 84: 321. 1928.

The effect of thyroidectomy on spontaneous activity was studied in 18 adult albino rats over a period of three months. The average daily activity after the removal of the glands was essentially the same as before. No objective evidence of lethargy was obtained, although the rats were in a definitely hypothyroid condition. Data from a number of other sources are considered bearing on the question of a possible relationship between the basal metabolic level and the amount of spontaneous activity shown by the animal. In 6 young adult female rats the feeding of thyroid gland substance caused a slight decrease in spontaneous activity. During the oestral cycle the changes in basal metabolic rate do not correspond with the changes in the activity level. Castration or spaying greatly decreases the activity, but decreases the basal metabolism comparatively slightly. The evidence is entirely against any idea that the amount of spontaneous activity manifested by an animal is dependent upon the basal metabolic level. Neither does the basal metabolic level show any close variation with the amount of spontaneous activity manifested.—M. O. L.

**The occurrence of a raised basal metabolic rate in new growth without hyperthyroidism.** Mason, E. H., *Canad. M. A. J.* 18: 681-682. 1928.

A patient with melano-sarcoma with extensive involvement of the liver had a consistently elevated basal metabolic rate of over plus 40%. There was no evidence of any thyroid disorder and no reaction to Lugol's solution.—A. T. C.

**Clinical and pathological evidence of the influence of iodine in the therapy of primary hyperthyroidism.** Menne, F. R., T. M. Joyce and J. D. Stewart, *Ann. Int. Med.* 1: 912-934. 1928.

A paper containing a history of the relation of iodine to the thyroid gland, advances in the medication of thyroid dysfunction and an analysis of 131 cases of primary hyperthyroidism. Four plates showing the effect of iodine administration on the thyroid gland are included. Though the ages of these cases varied (15-69 years), there were no differences in the clinical and pathological manifestations in these individuals. The prophylactic use of iodine has reduced the severity of the clinical symptoms. Iodine therapy



preoperatively increases the amount of colloid present in the thyroid gland. This accumulation of colloid probably inhibits the secretory function of the thyroid, which accounts for the beneficial effects of iodine preoperatively. The authors believe that the sudanophilic substance is concerned in hormone production.—E. L.

A case of exophthalmic goitre complicated with toxic adenoma treated by lead ionization. Miller, J., P. M. Macdonnell and A. F. G. Cadenhead, *Canad. M. A. J.* 18: 400-403. 1928.

Lead ionization accompanied by other treatment produced a marked diminution in the size of the gland and an improvement in the patient's general condition. Owing to the state of the heart surgical treatment was not considered feasible. From the post-mortem findings, notably from the degenerative changes found in the main portions of the thyroid, and from the relatively large amounts of lead (3 to 4 mgm.) it contained it is concluded that lead ionization was an important factor in the diminution in size of the thyroid. The foetal adenoma was easily separated and analyzed separately for lead; no trace was found.—A. T. C.

Influence of thyroid and insulin on the oxidases of the various organs. Mori, K., *Folia endocrinol. Japonica.* 2: 40-41, 122. 1927. *Abst., Chem. Absts.* 22: 460.

The oxidase content of the organs of the normal rabbit, especially of heart and kidney, is increased by insulin injections. A further increase is caused by the simultaneous injection of glucose. Thyroxin has the same effect on heart and kidney. The increase following the simultaneous insulin-thyroxin injection exceeds that produced by each hormone alone. The loss in oxidases caused by thyroidectomy may be made up by injecting insulin.

Action of thyroxin. Schoeller, W. and M. Gehrke, *Klin. Wchnschr.* 6: 1938. 1928. *Abst., Chem. Absts.* 22: 813.

Thyroxin produces only half the elevation in metabolic rate in castrated males as in non-castrated animals. A similar effect is not obtained in females. The normal female mouse is less reactive to thyroxin than is the normal male mouse.

Nodular goiter with hyperthyroidism. Thomas, H. M., Jr., *Arch. Surg.* 16: 117. 1928.

An analysis is presented of 32 cases of nodular goiter with hyperthyroidism in which exophthalmos was not present. The average basal metabolic rate was 38 per cent above normal. From his study the author concludes that all of these cases are instances of hyperthyroidism of a varying degree. Sections from the glands of

each case showed areas of hypertrophy and hyperplasia of the thyroid epithelium. The author divides the cases for study into two groups: patients less than 45 years of age, of which there were 13, and those of 45 years or more, of which there were 19. The glands from 11 of the 13 younger patients presented hypertrophy and hyperplasia of the thyroid epithelium of the variety seen in exoph-

thalmic goiter; in the other two cases of this group the diagnosis of hyperthyroidism was questionable.

In the older group (45 years or older) of 19 patients more or less slight degrees of hypertrophy and hyperplasia of the thyroid epithelium were found in each case. The author believes from a study of these cases that a slight degree of hyperthyroidism, when combined with other morbid conditions, may be sufficient to produce the clinical syndrome. Of this older group 11 patients suffered from heart disease, of whom 9 showed myocardial insufficiency and 8 of these also auricular fibrillation. Of the other 8 patients in this older group one showed primary hypertension (blood pressure 200/100), one showed an anemia of severe degree (hb. 55 per cent), two were obese and one, besides being obese, suffered from arteriosclerosis and hypertension (blood pressure 210/100). It is the author's belief that these factors, coupled with the advancing age of the patient, produce an individual who is more sensitive to slight degrees of hyperthyroidism and that these mild cases of hyperthyroidism (as estimated from the degree of hypertrophy and hyperplasia of the thyroid epithelium) become clinical entities only when coupled with some other morbid conditions. Where other morbid conditions were absent, namely, in the younger group, the degree of hypertrophy and hyperplasia of the thyroid epithelium equaled that seen in Graves disease.

The author concludes that these cases of nodular goiter with hyperthyroidism seem to differ from cases of exophthalmic goiter chiefly in the degree of thyrotoxicosis and occur mainly in elderly persons who are suffering also from other conditions which disturb their circulatory mechanisms.—Author's Abst.

# Endocrinology

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IODINE DEFICIENCY SYMPTOMS AND THEIR SIGNIFICANCE IN ANIMAL NUTRITION AND PATHOLOGY\*

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## INTRODUCTION

### REVIEW OF IODINE LITERATURE AND OBSERVATIONS, WITH PARTICULAR REFERENCE TO DOMESTIC ANIMALS

Although the cause and treatment of goiter in animals has in comparatively recent years engaged the attention of breeders and scientific workers, the disease has masqueraded under many colors and in many lands since ancient times. Vegetius in the fourth century observed goiter in draft animals and the Berber explorer, Leo Africanus, wrote lucidly of the goitrous and cowardly lions common to certain regions in the Atlas Mountains of Morocco. The effect of goiter in these animals was so marked as to perpetuate the old proverb: "Thou art brave as a lion of Alga, whose tail may be eaten by calves."

In more modern times we find that losses due to this disease have apparently increased, proportionately speaking. Due to

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modern developments in efficient sanitary control and prevention there has been a marked decrease in live stock losses because of parasites and infections. Hence diseases of different etiology have, to a considerable extent, been neglected. Today, however, many disorders having a distinctive nutritional basis are now enjoying the limelight. Now-a-days upwards of 60, 70 and in

SIMPLE GOITER  
DISTRIBUTION IN THE US

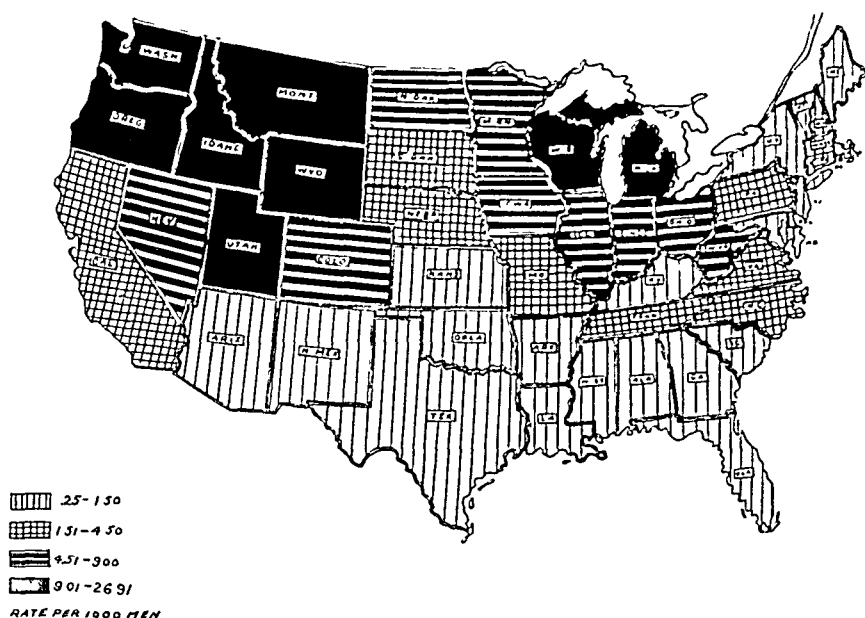


Fig. 1. Distribution of simple goiter in men—U. S. A. by states. (Drawn by us, based on World War Draft Board data of Davenport and Love, *Sci. Mon.*, January, 1920.) In some states, as Illinois and Pennsylvania, the goitrous condition in swine and sheep is reported more frequently from the northern portions. Compare Fig. 2.

some cases even close to 100 per cent of the pigs and lamb death losses are averted in certain districts. Efficiency in feed utilization is likewise often attained through the feeding of small amounts of iodine.

It is unfortunate that many authorities in the animal production field are still emphasizing hairlessness and "big neck" of the new-born as sole and distinctive symptoms of goiter. Although we are thankful for such outstanding signs, many cases of iodine shortage, not so distinguished or recognized, are being

wrongly diagnosed, hence progress in the promotion of animal health is hindered.

#### ETIOLOGY AND DISTRIBUTION OF GOITER

Stang and Wirth (1926) have pointed out that exophthalmic goiter does not normally occur in the lower animals; they further claim that it cannot be produced experimentally in an uncomplicated form. More important still, they emphasize that no cases have apparently been secured through the use of thyroid extract or the application of iodine feeding per os. These authors think that natural selection has probably eliminated the ordinary exophthalmic goiter from domestic animals, for in

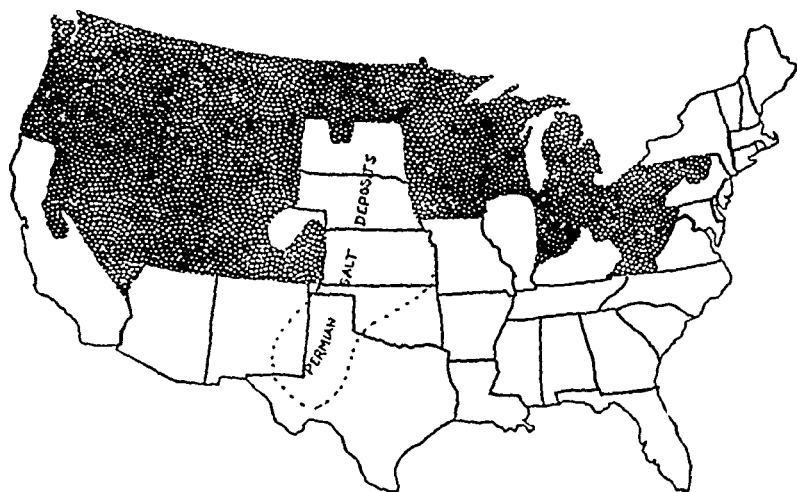


Fig. 2. Distribution of simple goiters in men U. S. A. geographically. Deduced from World War Draft Board data, courtesy McClendon, Hathaway and J. A. M. A. (May, 1924).

The area shown in black furnished soldiers every thousand of whom had from 5 to 111 men with goiters. A goiter in this case was defined as "too large to button a military collar around." Men showing slight goiter were passed and no record taken.

The Permian Salt Deposits shown in this figure were formed from the evaporation of sea water, which left extensive salt beds showing some iodine.

Compare Fig. 1, noting the general similarity. Fig. 1 shows four degrees of goiter prevalence; Fig. 2, goitrous and non-goitrous. The goitrous regions for domestic animals coincide, insofar as our observations go, with the human findings.

publications up to 1922 only 9 clinical cases were noted: 3 in horses, 2 in cattle and 4 in dogs. In 1923, a Basedow goiter was reported by Joest in sheep, but as yet no cases of hyperthyroidism have been reported in swine. On the other hand we have numerous reports of endemic goiters and cretinism in farm animals.

In North America, important foci for goiter are in the St. Lawrence river valley and Great Lakes basin where large numbers of lambs, pigs and dogs may be affected. In the Northern Plains region, extending westward from the Great Lakes to the Rockies on both sides of the International boundary, new-born pigs, lambs and other animals are especially subject to goiter; oftentimes, following winters of heavy snow, a large percentage of the spring pig crop is born hairless. The goitrous condition, however, is more often sporadic than endemic. Finally, one of the most important endemic areas is the Pacific Northwest, especially in Oregon, Washington, Montana, Alberta and British Columbia. In certain intermountain valley sections it has been

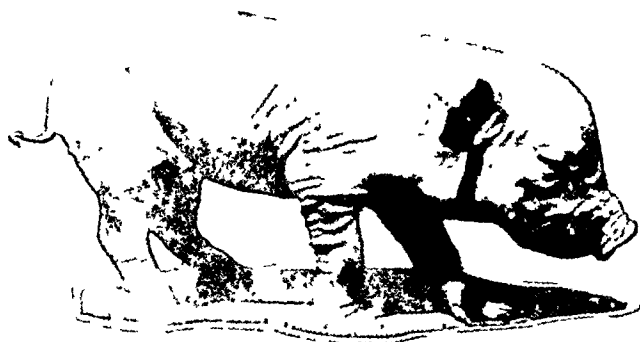


Fig 3 Hairless pig from state of Washington (close view) Note signs of weakness—droopy eyelids unstable balancing and extended position of front toes

well nigh impossible successfully to raise young stock of any domestic species because of the incidence of marked thyroid hyperplasia.

#### SYMPTOMS OF IODINE DEFICIENCY

The goitrous symptoms of pigs and lambs will receive major emphasis. In the iodine deficient territories represented by the Great Lakes basin and the Northern Plains area it is the pigs, goats and lambs which are the most likely to manifest gross pathology, easily observable.

Kalkus (1920) gives a very brief and satisfactory review of iodine deficiency symptoms in pigs and lambs. These are supplemented with our own observations in the development of the composite picture presented.

So-called hairlessness in new-born pigs, the result of thyroid hyperplasia, is a peculiar manifestation inasmuch as the alopecia

in the litters is rarely complete, many stages being represented within one litter; less frequently does the whole litter show complete baldness. Then, too, sows which are litter mates and have received similar care may farrow dissimilar litters, one showing hairlessness, and the other exhibiting, on casual observation, apparently normal pigs.

Pigs with alopecia adnata are generally born alive but the great majority die within a few hours. A very few may live and after several weeks become, superficially speaking, apparently normal. Affected pigs, farrowed alive, always show weakness and loss of vitality, seemingly in proportion to the degree of hairlessness. If entirely bald, they usually lie on their sides



Fig 4 A goitrous nanny goat from Pacific Northwest

unable to get onto their feet to suckle. If disturbed they squeal complainingly, in a peculiarly "dejected" and suppressed manner.

The skin of these pigs is thickened, pulpy and very tender. Bruises develop a livid red color, due to congestion and hemorrhage, and rarely do they heal satisfactorily. The pigs are in most instances seemingly quite fat (apparently adematous), often of good size and are generally carried in utero somewhat longer than normal.

Autopsies generally, although not invariably, reveal thyroid enlargements. Kalkus reports the average weight of thyroids

as 646.6 mgm. for normal pigs, although an abnormal pig may have glands weighing only 200 mgm. compared to a weight as much as 380 mgm. for normal thyroids. In no instance was the thyroid gland of pigs sufficiently large to be externally observable.

Histologically, the thyroid change in hairlessness is not always easily recognized. At times colloid material may be observed, but generally there is a degeneracy showing widely separated and irregular tubules with the intercellular spaces filled with serum, leucocytes, fibroblasts, extravasated blood and exfoliated follicle or acinic cells. Even these symptoms are sometimes absent. Other organs, too, may be affected, more often the heart, which seems to be dilated with a fatty degeneracy



Fig. 5. A group of goitrous kids, showing mohairlessness, from Pacific Northwest.

of the muscular tissue. Less often hemorrhages are present in the kidneys, intestines and heart, and serum accumulations in the thoracic and abdominal cavities.

The thyroid glands in sows farrowing hairless pigs are usually enlarged, oftentimes greatly so. Hart and Steenbock (1918) found the abnormal thyroid gland of a 300-pound sow to be the size of a man's fist, much larger than the "walnut-sized" normal gland. The iodine content of affected glands is practically always much below that of normal glands.

Alopecia adnata is not a universal symptom of iodine defi-



ciency. Oftentimes the pigs may be completely though thinly haired, and quite strong at birth. Yet such pigs often develop iodine deficiency symptoms shortly after farrowing. In many cases, the diseased condition is accompanied with manifestations of diarrhoea (scours), loss of appetite, slow growth, roughness of coat and other untoward symptoms.

The feeding of iodine carriers to the sows (which presumably transfer some of the iodine to the milk), or directly to the pigs, often brings about a slow return to normality.

At times, however, congenital cretinism may appear, in which case the pigs, although farrowed apparently normal, rapidly become cachectic even though they suckle with eagerness. If such pigs live they are most likely to become mis-shapen, ugly

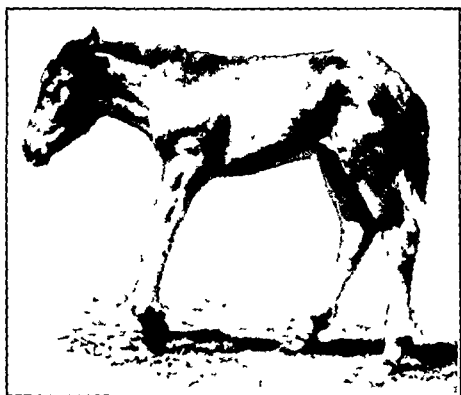


Fig 6. A goitrous foal, showing contraction of flexor tendons in forelegs. Note lowered head position, a sign of weakness

and oldish in appearance, very rarely attaining normal weights. Iodine therapy seldom if ever corrects the malady, although recoveries have been reported to us, following continued feeding of small dosages of desiccated thyroid gland. In such cases we suggest the experimental use of iodide and desiccated thyroid administration to the sows during pregnancy. Cretinism in swine should, however, be considered with an open mind until it is more completely investigated under carefully controlled conditions.

In the experience of Kalkus (1920) with lambs born in the State of Washington, in markedly goitrous regions, the affected glands are not generally large enough to be externally

discernable, although we have observed glands as large as an orange with smaller ones the size of hens' eggs. Glands as large as these are, in his observations, comparatively rare. The lambs may or may not be wool-less, the former condition being comparatively infrequent. Wool-less lambs rarely live long.

The observation of Kalkus in regard to the size of the affected thyroids in lambs is contrary to our experience in the Middle West. It may be that the breed of sheep is a factor inasmuch as certain characteristics of fine woolled breeds (Merinos and Rambouillets), with heavy skin wrinkles and protruding wool in the cervical region, hide or mask the thyroid



Fig. 7. Weak, goitrous foal in recumbent position. Note relative inability to raise head, drooping ears and eyelids and extended rear legs.

hyperplasia. Then, too, there is the possibility that some breeds may require less iodine for normal metabolism than others. In new-born Hampshire lambs we have frequently observed large goiters, but this breed is remarkably free from wrinkles of loose skin at the neck.

Histologically, the enlarged glands show small amounts of colloidal material or none. In marked hyperplasia the glands are in some cases very soft. In the degenerated gland one may find exfoliated columnar epithelial cells in the lumina, smaller lumina, and unevenly sized follicles.

The percentage of iodine content in the affected glands is generally much below that of normal glands, but the proportion of the iodine present does not necessarily decrease as the weight of the gland lessens. Changes in other organs are very similar

to that reported as found sometimes in pigs, namely, dilation of heart and hemorrhagic areas—notably on the kidneys, liver, pericardium and in lymph nodes. Extensive edema is oftentimes noted in the subcutaneous tissues.

Goats are affected in much the same way as sheep, but the goiters are usually larger.



Fig. 8. Goitrous calf with apparently healthy mother from province of Alberta, Canada. Note the goiter in the well-baited calf. Autopsy on mother would probably reveal a damaged thyroid.

Kalkus also reports many cases of goiter in both adult horses and new-born colts. On certain ranges from 30 to 50 per cent of all adult horses had visibly enlarged thyroid glands. These animals did not seem to be inconvenienced in any way insofar as their general health was concerned. In the new-born foal, however, the goitrous condition was extremely fatal. The affected colts were usually born alive, being well developed in physical body. From 75 to 90 per cent of the colts may be affected, and approximately 95 per cent of such animals are either still-born or die shortly after birth.

In most instances when seen in the recumbent position they

appear normal, although in some cases the lack of vitality is easily discernable even in this position inasmuch as the foal rests its nose on the ground with eyes half closed and ears drooping. The hind legs are extended, instead of lying forward underneath the body. However, when the colt attempts to rise marked weakness is observed. They are rarely able to stand unassisted because of a decided contraction of the flexor tendons in the fore legs, which causes a knuckling-over. An extension of the flexors of the hind legs was likewise observed. This latter condition causes the animal to stand on the posterior part of the fetlocks.



Fig. 9. Calf with gross goiter from Pacific Northwest. Note partial alopecia and droopy eyelid.

The breathing may or may not be labored. The badly affected animals usually live from one to three days, gradually becoming weaker until death relieves without a struggle.

A careful autopsy of four weak colts did not reveal marked enlargement of the thyroids. In three of the colts the enlargements were so slight as to be hardly discernable, and in the fourth instance the thyroids were approximately as large as hens' eggs.

Very few changes were noted in other organs. Although all cases showed contractions of the flexors in the fore legs and

extension of the same in the hind legs, the bones were apparently normal.

Goitrous calves are also prevalent in some districts. The calves are weak, and oftentimes show "big-necks." Autopsies reveal changes quite similar to those noted for lambs.

Kernkamp (1925) reports several instances of goiter in poultry. As yet only a very few cases have been observed. The affected birds were not suspected of being goitrous until dressed for the table, when the enlarged thyroids were noted. Histologically the thyroids presented enlarged acini filled with colloid material.

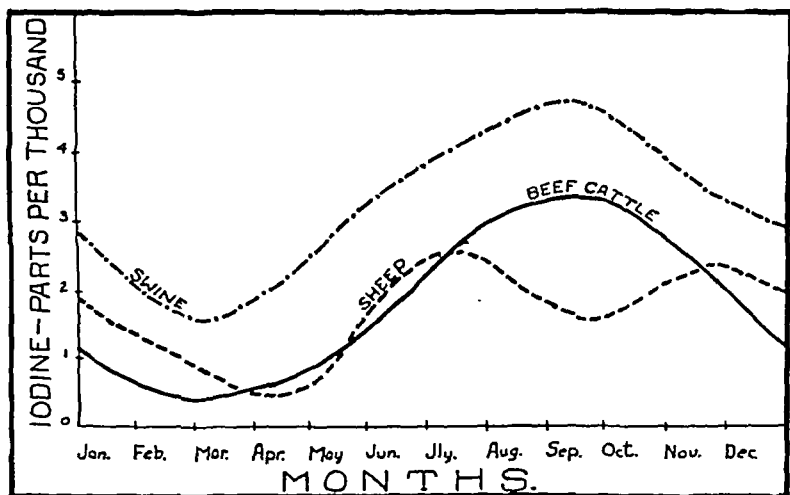


Fig. 10. Chart showing iodine, by months, in thyroids from Chicago slaughtered sheep. (Drawn and adapted by us from data of F. Fenger, Jour. Biol. Chem. 13:1913.)

Note correlation between grazing time on pasture in summer season and iodine content; the glands store iodine when animals graze. Note dip in sheep beginning July; our interpretation of this decline is that a relatively larger proportion of sheep arrivals in Chicago, July to October, come from the iodine deficient or goitrous states of Nevada, Idaho, Oregon, Washington, Montana, and Utah. These curves suggest that if desiccated glands of high iodine content are desired for therapeutic use that, at Chicago, swine or beef cattle thyroids should be selected in August, September and October, and sheep ones in July and perhaps in December.

#### SOURCES OF IODINE IN NATURE

This topic has been handled so ably and fully by many investigators—McClendon, Marine, Forbes, Von Fellenberg and others, that we shall limit our discussion mainly to a correlation of their findings with common farm practices.

If added dosages of iodine compounds are not fed to animals, the degree of iodine deficiency, if any, depends on the iodine content of natural feed stuffs, including water. In the case of animals which consume more or less dirt, as do swine in their rooting and herbivora in their grazing, the composition of the soil is a factor. The previous store of iodine in the body bears on the problem of deficiency.

The quantitative content of iodine in natural feed stuffs varies markedly. In general, the country may be divided into three regions: The region of sufficient iodine resources, extend-



Fig. 11. Salt is a good iodine carrier for efficient administration. All classes of livestock, particularly herbivora, take readily to salt in fairly regular fashion, hence by mixing the iodide with this essential nutritive substance the chances of regular ingestion are extremely favorable.

ing southward along the Eastern Appalachian slope across the Southern prairie belt to the Pacific coast. The semi-sufficient area confined to the east Central and Middle-western states excepting the areas immediately surrounding the Great Lakes basin. Finally, the territory of inadequate iodine supply elsewhere identified in this paper as an area of endemic goiter.

Losses due to goiter in the area of sufficient iodine supply are apparently very small. The abundancy of iodine may be assigned to a heavy rainfall and closeness to the ocean. Iodine is universally found in nature; due to the vaporizing property of this element there is a persistent evaporation of iodine from the ground to the atmosphere and with the precipitation of rain and snow this atmospheric iodine is again carried to the ground and perhaps to the sea. Regions near the ocean which have a relatively abundant rainfall are more apt to retain their iodine resources. On the other hand, certain inland areas with only a

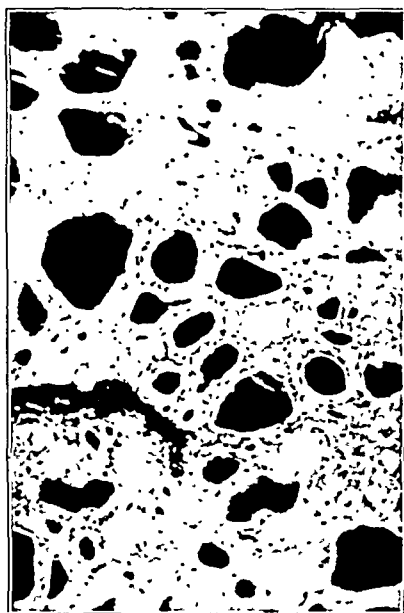


Fig. 12. Thyroid of normal swine. Note uniform follicular distribution; also colloid in follicles. (X125.)

small annual rainfall and a long distance from the ocean soon, geologically speaking, lose their natural iodine store. When evaporation exceeds the rainfall, particularly when the precipitation is heavy and the drainage light, the iodine stores in the soil are likely to be relatively high.

The area with a relative abundance of iodine has a temperate climate allowing extensive grazing by all classes of animals. This tends to promote the ingestion of a bulky herbaceous

of probable importance when he reports that the beginning of the embryonic thyroid development synchronizes exactly with the development of the Islets of Langerhans of the pancreas. All species studied reacted alike.

Hunziker (1928) advances a new theory covering the iodine requirements of animals, basing his interpretations on the following data from Von Fellenberg:

**IODINE CONTENT AND THYROID WEIGHTS OF VARIOUS BREEDS OF CATTLE**

Breed	No animals	Average live weight, Kgm.	Ave. weight of thyroids per 100 Kgm live weight, mgm.	Average iodine content per 100 Kgm live weight, mgm
Simmenthaler	12	562.5	6.80	0.86
Shorthorn	5	510.0	8.00	1.60
Braunvieh	5	332.0	14.05	3.47
Norweger	4	314.0	17.70	2.36



Fig. 14 Same as Fig 13 Specimen magnified (X500.)

He introduces substantially the following observations and conclusions: The heavier the average weight the smaller the thyroids and the lower the iodine per unit of live weight. The reason for this correlation probably lies in the effect of the thyroid extract on metabolism. Nevertheless metabolism, especially



the rate of metabolism, must be based essentially on the needs of the animals. This is primarily limited by the extent of the heat needs of the animals, which in turn is limited by the extent of the heat-radiating surface of the animal. The weight gain increases at a "cube" rate, while the corresponding surface area gain is at a "square"; therefore, if a close correlation (multiple, of course) is determined, covering mass, surface, thyroid weights and iodine content (thyroids), a good many enigmas may be cleared up.

Briefly, we may conclude that iodine and the thyroid glands

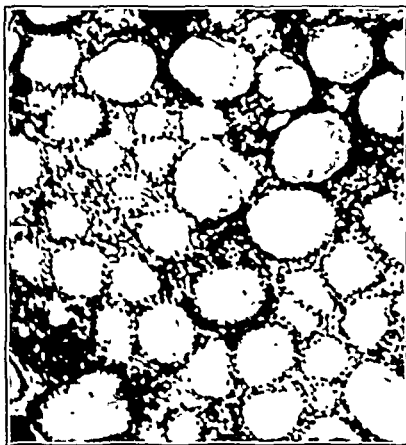


Fig. 15. Normal thyroid of a lamb. Note regularity of size and distribution of follicles filled with colloid, uniform cuboidal epithelium of follicles. ( $\times 125$ .)

play a fundamental and far reaching role in regulating the "metabolism rate" and especially in the economy of feed utilization. The latter premise will be developed more completely in a study of contemporary controlled feeding experiments with farm animals.

#### IODINE FEEDING EXPERIMENTS

Although a number of instances are reported in the literature wherein the administration of iodine to pregnant animals has prevented the birth of goitrous new-born animals, only a very few carefully controlled experiments are reported giving quantitative as well as qualitative results.

Among the former Kalkus (1920) reports field trials in

which tincture of iodine was furnished to ranchmen in return for certain birth records. Twenty-five stockmen treated collectively 77 mares, 137 cows, 28 sows and 66 sheep. In no case were goitrous young produced, although the same stockmen had previously suffered considerable losses due to goiter.

Hart and Steenbock (1918) report the feeding of 10 grams of potassium iodide per 100 pounds of a balanced basal ration to a sow which had previously farrowed three litters of hairless pigs on a similar or nearly similar ration without any incor-

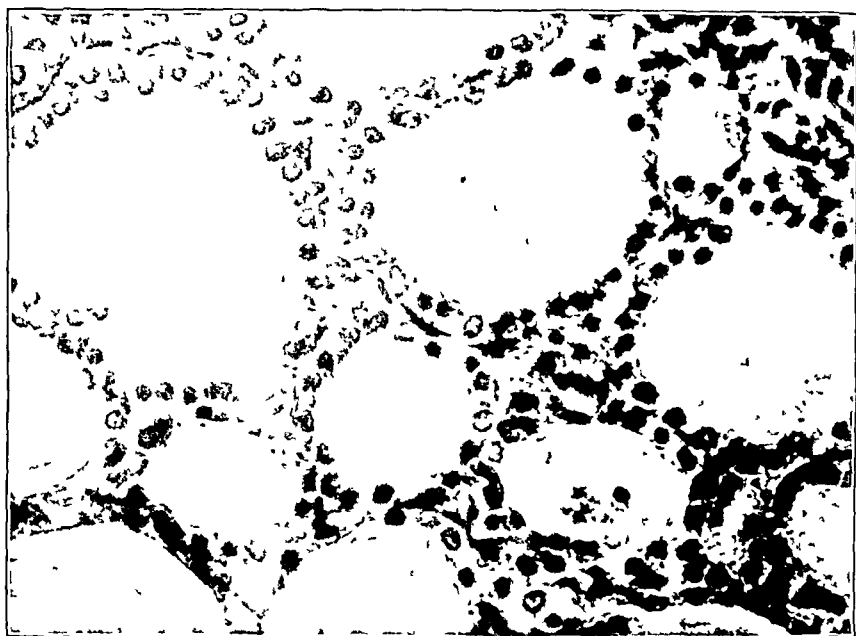


Fig 16 Same as Fig 15 Specimen magnified (X500)

porated iodide. The fourth litter appeared to be normal in every respect. This evidence indicates that iodine therapy prevented hairlessness.

As yet we know relatively little, from the standpoint of controlled experimentation, as to the preferable form and amount of iodine that should be fed. However, at the Iowa Agricultural Experiment Station we have had good results feeding potassium iodide in amounts equal to 0.00023 grain daily per pound of sow instead of the 0.00308 grain daily which Hart and Steenbock fed in the average sow's ration. The quantitative necessity of the added iodide is of course largely dependent on

the amount of iodine carried in the basal ration. Hansson (1927) reports European stockmen as feeding up to 0.00771 grain daily per pound live weight, although he recommends—based on Von Fellenberg's findings—a much smaller amount for maintenance, namely, about 0.00003 grain, plus additions to be regulated according to the specific nature of the production.

A rather closely controlled experiment has recently been reported by Weiser and Zaitschek (1927) who fed two comparable groups of sows a similar basal organic and mineral ration with the exception of a potassium iodide allowance to

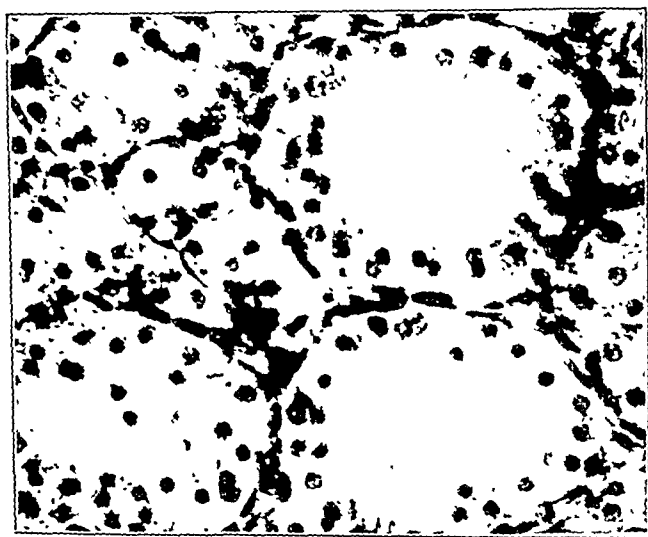


Fig. 17. Thyroid of goitrous lamb. Note absence of colloid, desquamation and columnar epithelium lining of uneven follicles. (X500.)

one group. During the last three weeks of gestation and also during the suckling period the sows, which were to farrow late in November and early in December, were fed a corn, barley meal and fish meal ration (changed somewhat later in the period). To the check group, I, was fed 50 grams (about 0.1 pound) calcium carbonate daily per sow. The other group, II, received the same mineral allowance except that it contained 0.25 percent potassium iodide (125 milligrams daily or about 0.0139 grain per pound of sow daily). The vital statistics for the two groups during the farrowing and suckling periods are:

	Group I Not fed iodide	Group II Fed iodide
No. of sows .....	17	23
Duration of gestation period, days.....	116	114
Number of pigs per litter, average.....	8.94	9.13
Average birth weight per pig, lbs.....	2.82	2.55
Total number of pigs.....	152	210
Born dead, percent.....	0.66	2.85
Smothered, percent.....	2.63	11.45
Died of disease, percent.....	54.61	2.85
Weaned, percent.....	42.10	82.85
Average weight of pigs, lbs.:		
At birth .....	2.82	2.55
At 4 weeks.....	11.64	12.87
At 6 to 7 weeks.....	15.22	23.10
At weaning time (10 weeks).....	28.97	40.79
Minimum .....	19.80	26.40
Maximum .....	34.56	55.37

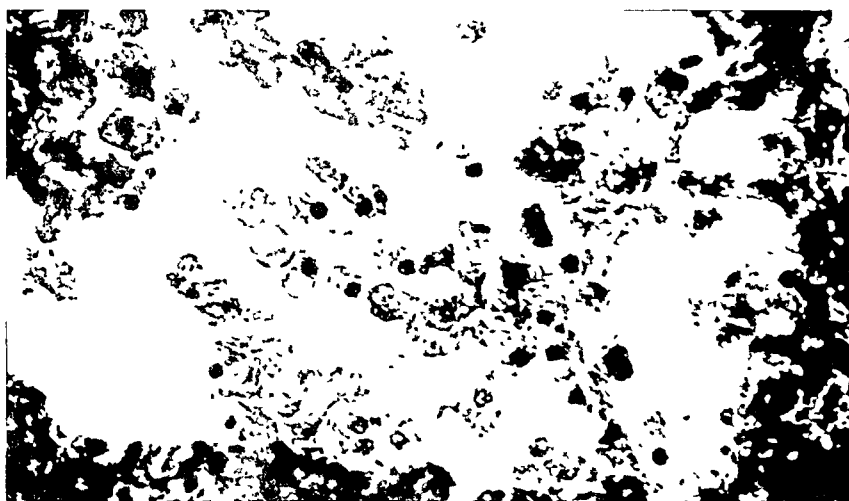


Fig. 18. Thyroid of another goitrous lamb. Note exfoliated cells in abnormal single follicle. (X500.)

These data show that even in so short a time as three weeks before farrowing enhanced results were gotten by feeding iodine. Note particularly the difference in the percentage of pigs weaned, namely, 42.10 for the non-iodide fed sows and 82.85 for iodide fed sows. Also note the "quicker" gain in weight, the final weight being nearly 41 percent in favor of the iodide fed pigs at ten weeks of age.

These investigators also fed the iodized calcium carbonate to a group of 50 pigs farrowed in early October. These pigs had been making subnormal growth and were rapidly dying in

spite of conscientious care. The selections were made after weaning and they were then placed on the basal ration plus iodide. In less than ten days the death losses stopped and the remaining pigs quickly regained their appetite and health, so much so that in a very short time they appeared normal in every way.

Kalkus (1920) has also reported a pertinent experiment in the control of goiter in goats. The tabulated results are as follows:

RESULTS OF IODINE TEST, 1917-18  
(6 Does in Each Lot)

Lot	Form of Iodine Compound	Dosage	Frequency and Method of Administration	No. of Young Born	Condition of Young at Birth
I	None	.....	.....	10	All hairless 8 still born 2 died shortly
II	KI	2 grains in $\frac{1}{2}$ oz. water	Daily during gestation period, per os	5	All normal
III	Tincture of iodine	5 mls. of 10% sol.	Weekly during gestation, subcutaneous	7	All normal
IV	Tincture of iodine	1 ml.	Weekly during gestation, on back	8	7 normal 1 slight thyroid enlargement, but well haired

These results indicate that the method of application is of minor importance in the prevention of major gross symptoms.

Bowstead (1925) reported an experiment carried on in the Province of Alberta, Canada, in which two lots of pregnant ewes were fed a similar basal ration with and without potassium iodide. A third group had lime added, but without iodide. The daily basal ration per sheep consisted of approximately 3.3 pounds of oat hay; 0.3 pound of barley grain and self-fed salt. The potassium iodide was allowed with the salt, the mixture consisting of five ounces of iodide to each 100 pounds of salt.

The check group of ewes lost 25 pounds per head on the average during the pregnancy period and 83 per cent of the lambs showed goitrous symptoms, partial wool-lessness being observed. The group receiving the potassium iodide addition lost only 17 pounds per individual on the average and none of the new-born lambs showed any gross symptoms of goiter. Small additions of lime without potassium iodide were without curative properties inasmuch as 92 per cent of the lambs from this group of ewes showed goiters. The lime addition, however, improved

the nutritive qualities of the ration in that the average ewe lost but 7 pounds in weight.

In the summary of the experimental results, Bowstead emphasizes that the feeding of potassium iodide resulted in almost 100 per cent strong and thrifty lambs. These averaged about one pound (nearly 12 per cent) heavier than those of the two groups not fed iodide.

#### THE EXPERIMENTAL FEEDING OF IODIDE TO SWINE

The positive results secured from the feeding of iodine to pregnant swine in the prevention of hairless pigs and allied con-



Fig. 19. Thyroid of goitrous new-born foal. Note numerous small tubules and colloid absence. (X125.)

ditions are outstanding. Alopecia adnata in the young swine is now being widely prevented when the cause is of nutritional origin, this by the feeding of an iodine carrier. To infer, however, that an iodine deficiency is not being experienced in swine herds if hairless or semi-haired new-born pigs are not evidenced is illogical. Well-haired pigs may, in our judgment, be the rule at farrowing time, and yet there may be an insufficiency of iodine for normal metabolism.

It is unfortunate from the standpoint of veterinary and farm practice that it is so difficult to detect enlarged thyroids or simple goiters in swine. In the present state of our knowledge we do not have any practical way of knowing exactly whether or not any specific farm is laboring, from the swine standpoint, under iodine deficiency. However, if the farm under inspection is in a goitrous or semi-goitrous area, or if goitrous conditions have been noted in other types of stock, it is pretty good policy to resort to iodine feeding as a matter of sensible insurance protection.



Fig. 20. Same as Fig. 19. Specimen highly magnified (X500.)

In the experimental swine herds at the Iowa Agricultural Experiment Station we have never had, in the eighteen years of the author's experience, any hairless pigs at farrowing time which could be attributed to iodine deficiency. On the other hand, goiter has been experienced frequently in the new-born lambs of the breeding flock. The latter fact indicated that there might be an iodine deficiency prevalent in the swine herd. We inaugurated experiments in order to determine if the addition of iodide to ordinary rations fed to swine on grass or in winter

dry lots would yield favorable results, physiologically and economically speaking.

#### FEEDING IODINE TO GROWING SWINE PROVES BENEFICIAL

In Table I are presented some results secured in three years of experimentation with young, growing pigs, fed with and without iodide additions to the basal rations.

The experiment was conducted on rape pasture. The basal ration fed was a standard one composed of corn grain, mostly yellow, "60 per cent protein" meat meal tankage, corn gluten meal, corn oil cake meal, linseed oilmeal, cottonseed meal, bone meal, and flake salt. This was full-fed to Group A in Experi-



Fig. 21. Normal thyroid of cow. Note regularity of follicles and presence of colloid.

ment I. Group B, in the same experiment, was fed exactly the same, with the exception that a small allowance of potassium iodide was made, the iodide being mixed with the basal feed.

The growing and fattening swine on experiment showed no external evidence of iodine deficiency insofar as visual observation for specific abnormalities was concerned. However, Group B gained practically 8 per cent more rapidly and took 55 pounds less feed for the hundredweight of gain produced.



In Experiment II the basal ration was changed somewhat, consisting of corn grain, mostly yellow, cottonseed meal, blood meal, "high calcium" limestone, bone meal and flake salt. This was full-fed to Group A. Group B was fed the same excepting that potassium iodide was added. In this experiment we saw no gross signs of goiter even though careful observations were again made. Nevertheless, the iodide fed pigs gained more rapidly, practically 9 per cent more, and the feed requirement was close to 10 per cent less, 40 pounds below the check group.



Fig 22. Same as Fig 21. Specimen highly magnified. Note the orderly, artistic biological architecture, and interfollicular elements (X500)

This experiment was conducted in the summer under pastureless conditions.

In a later year we again studied two groups of pigs under winter conditions. In this experiment the check ration consisted of eleven commonly used farm feeds. It was thought that the chances for iodine deficiency might be less if a wide variety of feeds were incorporated in the basal ration. Nevertheless, the results secured were similar to other years, the gains being faster, some 13 per cent more, and the feed requirements per hundredweight of avoirdupois produced on the pigs less, approxi-



mately 8 per cent. In this experiment no gross signs of a goitrous condition were noted.

The three year average showed that when a small amount of potassium iodide, from 0.08 to 0.67 grain of potassium iodide per pig daily, was fed the animals made 10 percent greater daily gains with a resultant saving of 10 per cent of the feed per unit of weight increase produced. Thus it may readily be seen that even under seemingly healthy conditions the controlled experi-



Fig. 23 Thyroid of new-born goitrous calf. Note disruption of follicles, connective tissue elements and extravasated, non-nucleated red blood corpuscles. (X500.)

ments revealed the fact that the addition of a small amount of iodide in the porcine rations increased the metabolism in a favorable manner, augmenting the gains and conserving the feed.

The greater growth evidenced by the iodide fed pigs was not only in weight but also in dimension. Careful measurements revealed the fact that, in Experiment II, the pigs grew longer and taller in the same period of time, when iodine was administered. The statistical interpretations of the data in these three experiments demonstrate quite conclusively that the results secured, with the differences in favor of iodide feeding, were significant.

## EXPERIMENTS IN THE FEEDING OF IODINE TO SHEEP

In the spring of 1917 a number of new-born lambs, 23 out of 55 produced by 40 breeding ewes, showed noticeable enlargement of the thyroids. The ewes were fed in four groups, each group receiving a different ration. Every group produced goitrous new-born lambs. Fortunately, we had taken in the regular course of experimental procedure composite samples of the feeds used, and we found that iodine was present in only one of them. The rations fed were corn silage, timothy hay, oat straw, shelled corn, corn gluten feed and salt. Both the roughages and the grains were kept constant in quantity in each group fed.

The only feed carrying iodine was corn gluten feed; it containing 0.00011 percent. It is interesting to note whether or

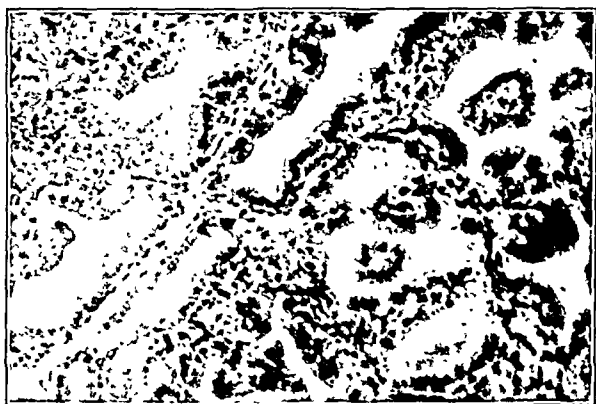


Fig. 24. Thyroid of goitrous calf six weeks old. Note absorption of blood extravasate, subsidence of congestion, new follicles in process of development and disrupted follicles. (X125.)

not its inclusion in increasing amounts in the daily ration per ewe protected against goiter to any extent. Two of the groups, receiving respectively  $\frac{1}{4}$  and  $\frac{1}{2}$  pound of the corn gluten feed, the remainder of the pound grain allowance being shelled corn, per ewe daily, showed an average of 51 percent of the lambs affected with goiter, whereas the use of 1 pound of the same feed, no corn being given, in a corresponding group resulted in only 40 percent of goitrous lambs. The water which these ewes drank carried only 0.012 parts of iodine per billion, much

too low a proportion to be effective under such conditions of iodine shortage.

#### ANOTHER CONTROLLED EXPERIMENT IN IODIDE FEEDING WITH PREGNANT EWES

A carefully conducted iodide feeding experiment was made in the winter of 1917-18 with the same breeding ewe flock which had given birth to so many goitrous lambs in the previous year. The ewes were divided into four groups of nine animals each. All ewes received the same basal ration, both quantitatively and qualitatively speaking. The daily ration per ewe of all groups

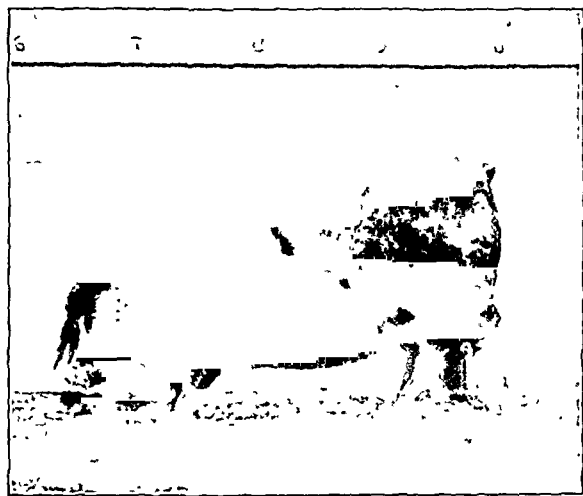


Fig. 25. Representative pig group A. Experiment II. No potassium iodide allowed. Compare Fig. 26.

was as follows: 0.25 pound shelled corn, 0.75 pound corn gluten feed, 2.00 pounds corn silage, 0.5 pound timothy hay, and 0.65 pound oat straw. All ewes were allowed to have access to iodine-free salt from the same source as that fed in the previous year when goitrous lambs were experienced in considerable number.

The daily dosage of potassium iodide per ewe daily was for the various groups as follows: Group A (check), none; Group B, 2.02 grains; Group C, 5.66 grains; and Group D, 6.09 grains. The dosages were purposely made large in order to find out if

any deleterious effects might result because of such liberal allowance. The iodide feeding covered a period of approximately two and one-half months during the pregnancy period.

No palpable goiter was observed in either the ewes or the young during the experiment, although the animals were examined frequently. Neither was iodism noted in any of the iodide-fed groups.

The same basal ration fed the previous year did not, however, protect against goiter, as we have hereinbefore shown. While the feeds fed were the same by name, the source was not

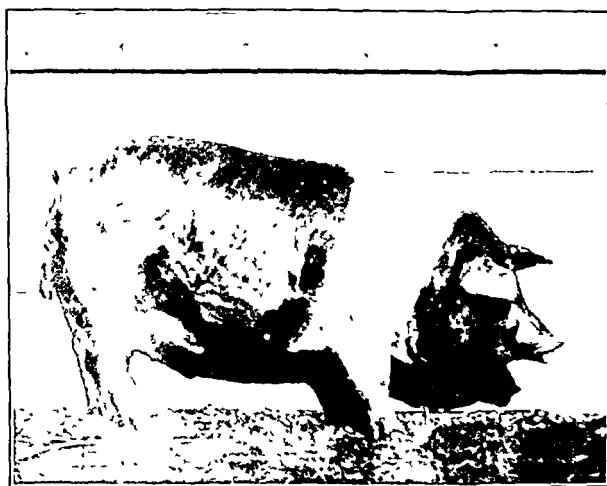


Fig. 26. Representative pig group B. Experiment II. Potassium iodide fed. Compare Fig 25. Note sleeker coat and signs of more vigor.

identical with the previous year. We have found in this as well as through previous experience that feeds of the same kind may vary considerably in their iodine content even though produced under so-called similar conditions.

Some factor, more likely factors, as yet not understood alter the iodine content of the feed. Of course it is known that feeds produced in goitrous regions run on the average considerably lower in iodine than similar feeds, the products of goiter-free areas. Possibly such factors as the amount of rainfall, its distribution, the temperature, the character of the soil, and others may be thought of. The only way to be sure whether or not any one feed carries a sufficiency of iodine is to analyze it.

Table II carries data pertinent to our experimental inquiries; an interpretation of this table suggests the following:

1. There was very little difference in the average daily gain of the ewes in the various groups.

TABLE II

THE FEEDING OF EXCESSIVE DOSAGES OF KI TO PREGNANT EWES PROVES  
DETRIMENTAL TO LAMBS

Four Groups of 9 Ewes Each  
Potassium Iodide Fed for Approximately 2½ Months  
Winter, 1917-18

Group No.	Potassium Iodide per Ewe Daily Grains	Average Daily Gain per Ewe Lbs.	New-Born Lambs Produced	Average Vigor of Lambs 100% = Perfect	LAMBS		
					Died at Birth %	Dying Before Two Months Old %	Total Deaths %
A	None	0.19	14	90	0	7	7
B	2.62	0.22	14	74	0	13	43
C	5.66	0.18	15	60	20	60	80
D	6.09	0.23	13	48	23	69	92

2. The average vigor of the new-born lambs was affected adversely by the high dosages of iodide. As the doses increased

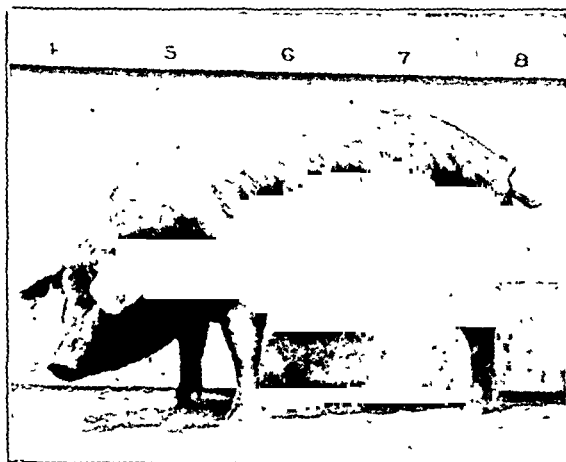


Fig. 27. Representative pig group A. Experiment III. No potassium iodide fed. Compare Fig. 28.

from 2 to 6 grains per ewe daily the average vigor, based on 100 per cent being perfect, decreased from 74 to 48 per cent. And the check group, not receiving added iodide, showed for the new-born lambs 90 percent of perfect vigor. Apparently, the heavy ingestion of potassium iodide was detrimental to the young in utero.

3. The number of dead lambs at birth was largest in Groups C and D, the ewes of which groups received approximately 6 grains of KI per head daily, the percentage being 20 and 23 percent respectively. On the other hand, when only 2 grains was administered there were no dead lambs at birth; neither did the check group show any.

4. The loss of lambs during the recorded portion of nursing period, two months, was much greater when the iodide ingested was the heaviest. The check group, A, showed only 7

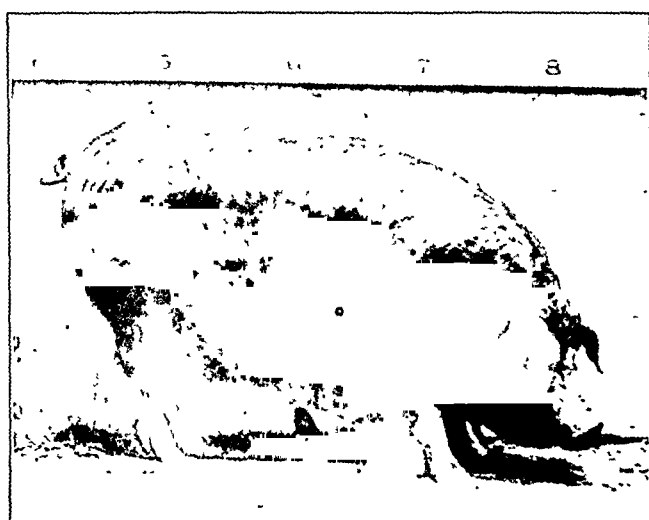


Fig. 28. Representative pig group B. Experiment III. Potassium iodide fed. Compare Fig. 27. Note greater size and weight.

percent deaths, whereas Group D, receiving the heavy allowance of 6 grains of potassium iodide, showed 69 percent deaths.

5. Many of the deaths among the lambs during the suckling period were due to hemorrhagic septicemia; the causal bipolar organisms were identified by Dr. Charles Murray of the Veterinary Division of Iowa State College. Since all of the new-born lambs were kept in the same paddock, the iodide administration being discontinued at parturition time with the rations thereafter being kept on the same basis for all groups, it appears that the heavy administration of iodine in the form of potassium iodide decreased the resistance of the young to this specific disease.



Since the experiment was conducted in series fashion, increasing amounts of iodine being fed as the groups ranged from A to D, it is believed that the increased toll from the hemorrhagic septicemia was correlated with the size of the dosage of iodide. To make this more plain we emphasize that Group A receiving no iodide lost only 7 percent of its lambs, Group B receiving more iodide, or 2.02 grains per head daily, lost 43 percent of its lambs, Group C receiving 5.66 grains, 60 percent, and Group D getting 6.09 grains, 69 per cent during the recorded suckling period. Since the big proportion of the

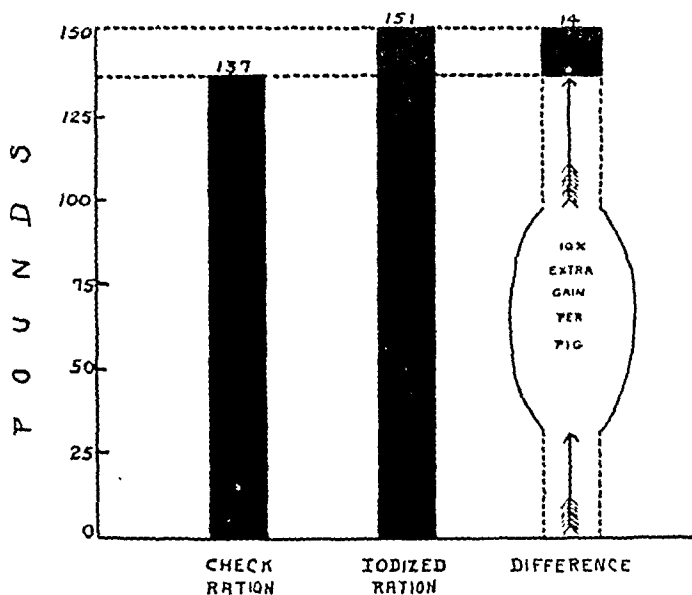


Fig. 29. Chart showing (graphically) relatively greater daily gain per pig of pigs fed potassium iodide in three experiments, I, II and III.

deaths occurred within two to six days after birth, we were suspicious that the milk of the ewes was altered by the iodide feeding, hence we made chemical examination to determine the facts. The results of these studies are given in Table III entitled "Iodine in Ewes' Milk Increased by Iodide Feeding."

6. Why did the heavy administration of iodide to pregnant ewes lessen the resistance of the new-born lambs to a certain disease? In the light of our latest experiments (see Tables IX and X, and discussion of them) it appears that dosages

of iodide during pregnancy in excess of the amount required for normal functioning of ewes and their new-born lambs decrease the size of the thyroids in the offspring, lower the amount of iodine per lamb thyroid and lessen the quantity of thyroidal iodine per unit of lamb weight. If marked successive excesses of iodide would further augment these trends, it may readily be seen that the thyroids of the new-born would become smaller and smaller, and further that the thyroidal iodine would diminish accordingly. Did such a process take place in the lambs of this experiment under discussion? Unfortunately, we did not study the thyroids of these lambs, so do not know. If such an atrophic and chemical change did take place, we might hypothe-

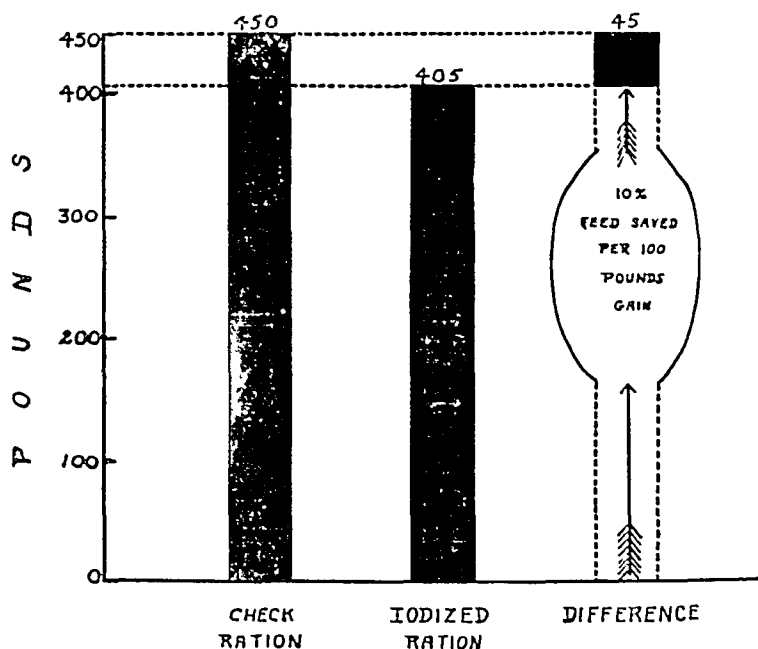


Fig. 30. Chart showing (graphically) relatively less average feed requirements per hundred-weight of increase made by the pigs fed potassium iodide in three experiments I, II and III.

size as regard the influence on the biological functioning of the thyroids of the unfortunate lambs stricken with hemorrhagic septicemia. Is it possible thus to reduce the thyroids of the lambs in utero and of the new-born in size and in iodine to the extent that they are injured severely enough that they do not function adequately in the protection of the organism? We shall proceed in future experimentation with new objectives in

mind, getting data that should throw light on the points involved in our questions.

TABLE III

IODINE IN EWES' MILK INCREASED BY IODIDE FEEDING  
*Iodide Allowance Discontinued on Parturition Day*

Group	Potassium Iodide per Ewe Daily (Grains)	Iodine in Milk Samples—Average					
		—Colostrum—		Post-Parturition			
		Samples	p.p.m.*	5 Days Samples	p.p.m.	15 Days Samples	p.p.m.
A	none	1	2.4	3	0.0	3	0.0
B	2.02	1	41.1	4	8.5	3	0.0
C	5.66	5	51.8	3	16.2	3	0.0
D	6.09	3	38.6	3	19.7	3	6.5

\*Parts per million.

#### IODINE IN MILK OF EWES

As the amount of iodide increased in the ewes' ration, so, too, did the amount of iodine increase in the milk (see Table

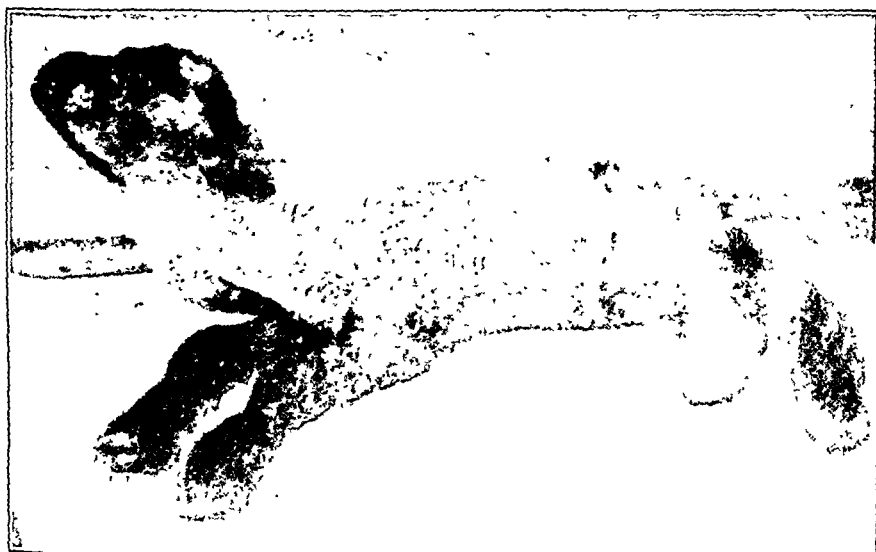


Fig. 31. Gross observable goiter of new-born lamb typical of many observed in our experiments. Larger and smaller goiters were experienced by our lambs on iodine deficient rations. The lambs having the largest goiters were practically always quite weak and the mortality was extremely high. Rapid heart beat and dyspnea was noted. Very small goiters were not externally observable or palpable.

III). The colostrum showed, in round numbers, 41, 55 and 39 parts of iodine per million parts of material, respectively, in the iodide-fed Groups B, C and D. Contrast these figures with 2.4, Group A, where no iodide was given.

Milk samples were again taken five days following parturition, with comparative results similar to those secured on the colostrum. The iodide feeding during the pregnancy period had its effect on the iodine content of these samples. After five days the milk from the check group showed no iodine, whereas the milk from Group D, 6 grains iodide allowance, showed 50 p.p.m.

At fifteen days the iodine had disappeared from the milk samples of Groups A, B, and C, but Group D, the heaviest iodide-fed group, still showed 6.5 p.p.m.

It is evident, therefore, that the lambs from the ewes heavily fed on iodide received extra liberal iodine supplies from their mothers' udders.

This experiment illustrates quite clearly the necessity of careful regulation of iodine feeding under some conditions; the evidence certainly points most suspiciously to the possible development of specific evil effects which may be experienced when too much potassium iodide is fed pregnant animals.

#### SUSCEPTIBILITY OF SEXES OF NEW-BORN LAMBS TO GOITER

We present in Table IV some data showing the occurrence of goiter, visually observable, in new-born lambs born in two different seasons—one quite goitrous, 1916-17, and another semi-goitrous, 1924-25.

It appears that the ewe lambs were more prone to this disease when the conditions of feeding and environment were similar. The data are too meager to warrant comment other than to state the facts, as has been done.

TABLE IV  
GOITER DISTRIBUTION BY SEXES IN NEW-BORN LAMBS  
Gross Goiters Observed

Observations	A Goitrous Season 1916-17			A Semi-Goitrous Season 1924-25		
	Rams 27	Ewes 28	Total Both Sexes 55	Rams 25	Ewes 33	Total Both Sexes 58
<i>Large Goiters:</i>						
Distribution, actual..	4	4	8	0.0	3	5
Distribution, percent- age of each sex or combination .....	14.8	14.3	14.5	0.0	15.2	8.6
<i>Medium to small Goiters:</i>						
Distribution, actual...	7	8	15	0.0	1	1
Distribution, percent- age of each sex or combination .....	25.9	28.6	27.3	0.0	3.0	1.7
Within the affected group .....	46.7	53.3	....	0.0	100.0	...
<i>Free from Goiter:</i>						
Distribution, actual..	16	16	32	25	27	52
Distribution, percent- age of each sex or combination .....	59.3	57.1	58.2	100.0	81.8	89.7

## SHEEP FEEDING EXPERIMENTS CONTINUED—LATEST SERIES

In the fall of 1925 we inaugurated a series of experiments with ewes and their lambs, covering an indefinite period of time. To date, 1928, three years' work have been done and many data of an enlightening nature now grace our archives.

Four groups of ewes have been fed, under comparative and controlled research conditions, on different allowances of iodine fed as potassium iodide. The iodide administered per ewe per day in these groups being, none,  $1/20$ ,  $1/5$ , and  $4/5$  grain during the major portion of the gestation period in each of three years.

Detailed records have been or are being gathered on the weights of ewes and lambs, feeds consumed and their iodine content, gestation period, wool yield, character of lambs, size of thyroids with their iodine yield, iodine percentage in the lambs' bodies, and other pertinent data. To date many of the chemical determinations are as yet incomplete, but such data as are available are discussed herein.

## HOW THE IODIDE FED EWES WERE HANDLED AND FED

The ration fed to the experimental ewes during the winter pregnancy season, in which time of the year only the potassium iodide allowances were made, was the same for all groups in any one year. In 1925-'26 the legume hay fed was soybean, but in the last two years, 1926-'28, alfalfa hay was substituted. The same amount of each feed fed the average ewe per group was kept quite constant not only in each winter season but for all years.

It is to be emphasized that the experimental conditions were controlled so as to make the iodide feeding, at different levels of intake— $1/20$ ,  $1/5$  and  $4/5$  grain per ewe daily—significant from the research standpoint. No other variants were introduced, hence the variations in the results secured, after allowing for the normal probable errors of such biological work, may be attributed to the effect of the potassium iodide allowances.

The rations fed per ewe daily were as follows:

*Lot I*—Grain Mixture A (shelled corn—natural moisture basis—60 lbs.; whole oats 30 lbs.; linseed oilmeal 10 lbs.), 1

pound divided into 2 equal feeds; 2.7 pounds of corn silage A.M. feed; 1 pound legume hay (soybean hay first year, 1925-'26, and alfalfa hay second and third years, 1926-'28), P.M. feed; and flake salt (mixed with Grain Mixture A) two times daily at rate of  $\frac{1}{2}$  ounce (0.03125 lb.) per ewe daily.

*Lot II*—Same as Lot I but  $\frac{1}{20}$  grain of KI fed with the salt.

*Lot III*—Same as Lot I plus  $\frac{1}{5}$  grain of KI fed with the salt.

*Lot IV*—Same as Lot I plus  $\frac{4}{5}$  grain of KI fed with the salt.

The iodide feeding was discontinued when parturition occurred, having been begun in the breeding season, at which time the ewes went into their winter dry lot quarters.

Cereal straw, practically all from oats, was used for bedding all groups: our observations were that they ate no bedding.

The ewes were diverted to a small paddock on dry, sunny and otherwise propitious days, for exercise and solar irradiation.

All groups were handled alike in common yards during the suckling period, receiving Grain Mixture A, alfalfa hay, corn silage and technical sodium chloride. The KI administration was discontinued on the birthdays of the lambs. The lambs during the first 60 days after birth were fed corn grain, whole oats and linseed meal, free-choice style in a creep. The roughages and grain were discontinued when the ewes' lambs were sixty days of age, and all were then turned as one flock to blue grass pasture during the summer and early fall. The lambs were weaned at about five months. In the late fall the ewes again went into the winter quarters when they were divided into groups and again fed as hereinbefore stated. The point we emphasize is that conditions were uniform for all ewes from winter to winter season, so that the iodide allowances fed represented the variables or experimental differences.

Table V gives data on the ewes and lambs covering number of each involved together with the weights and gains of the ewes and losses in ewe weight during parturition.

TABLE V

WEIGHT, GAINS AND LAMBING RECORD OF THE PREGNANT EWES  
(Three Years of Data)

Ewes Averaged 103.7 Days in the Winter Season of Iodide Feeding  
10 Breeding Ewes per Group Each Year—Averaging Approximately 154 Pounds  
at Start

Late November or Early December to Lambing Time the Following  
February and March

Group or Lot No. and Designation	No of Ewes Carried (3 Yrs)	No of Ewes Which Lambcd	Average Initial Weight of the Ewes Lbs.	Average Daily Gain per Ewe Lbs.	Loss of Weight per Ewe in Parturition Lbs.	New Born Lambs Produced per Group in the Three Years		
						Rams	Ewes	Total
I Check— No iodide	30	27	184 6	0 22	29 2	23	25	48
II KI, 1/20 grain	30	26	181 1	0 24	30 3	22	25	47
III KI, 1/5 grain.	30	25	186 0	0 20	27 5	21	18	41
IV KI 4/5 grain.	30	28	181 8	0 24	27 9	22	29	51

#### GESTATION PERIOD AFFECTED

The gestation period was apparently slightly lengthened through the addition of iodide to the partially iodine deficient basal ration as is evidenced in Table VI. The average period of all the check ewes, Group I, all years, was 145 83 days as contrasted with 146 16 days for Group II (1/20 gr. KI), 146 73 days for Group III (1/5 gr. KI), and 146 52 days for Group IV (4/5 gr. KI). The average of all of the iodide fed Groups, II, III and IV, shows 146 48 in comparison with 145 83 days for the check, Group I, all years, or a difference of 0 65 day. Biometrical analysis of the data indicate that if the experiments were duplicated during a three year program, under the same conditions, that the chances of Groups II, III and IV showing a longer period than the check group, I, would be respectively 77, 96 and 95 percent, i.e., 77, 96 and 95 times out of a hundred. Statistically, therefore, the longer periods of gestation encountered in our investigations to date appear to be of significance. It should be borne in mind, however, that the comparisons made by us cover the relationship existing between ewes having on the one hand a partial deficiency of iodine in their feed and water intake sufficient to cause, approximately, a doubling of the weight of the thyroid, a moderate hypertrophy; and on the other hand, ewes having an apparent sufficiency of iodine for normal reproduction.

Kalkus (1920) in comparing the gestation periods of 45

TABLE VI  
GESTATION PERIOD BY YEARS  
(Averages by Groups, Annually and for Three Years)

Group No. Year	I (Check)			II (1/20 Gr. KI)			III (1/5 Gr. KI)			IV (4/5 Gr. KI)			All Iodide-Fed Groups, II, III and IV, Consolidated		
	No. Ewes Lambled	Average Gestation Period (Days)	No. Ewes Lambled	Average Gestation Period (Days)	No. Ewes Lambled	Average Gestation Period (Days)	No. Ewes Lambled	Average Gestation Period (Days)	No. Ewes Lambled	Average Gestation Period (Days)	No. Ewes Lambled	Average Gestation Period (Days)	No. Ewes Lambled	Average Gestation Period (Days)	No. Ewes Lambled
1925-26.....	10	146.53	7	146.82	9	146.92	10	146.51	26	146.74	26	146.74	26	146.74	26
1926-27.....	8	144.97	10	145.35	9	146.82	9*	146.21	28	146.10	28	146.10	28	146.10	28
1927-28.....	9	145.80	9	146.54	7	146.50	—	146.84	25	146.64	—	146.64	25	146.64	25
Total.....	27	145.77	26	146.24	25	146.75	28	146.52	79	146.50	79	146.50	79	146.50	79
Av., straight†...		145.83 ± .20		146.16 ± .22		146.73 ± .28		146.52 ± .20		146.48 ± .12		146.48 ± .12		146.48 ± .12	
Av., weighted§..															

\*One abortion (cause unknown) not included; time, 83.41 days.

†Averaging the average periods of each year.

§Averaging all of the gestations—this being the actual average for all years.



ewes giving "normal births" with 8 ewes presenting "goitrous births" found 151 and 153 days respectively. The range in the normal ewes was 16 days and in the affected ones 14 days. Goats in his experience had longer pregnancy periods when the kids were affected with goiter, 19 normals averaging 145 with a maximum range of 32 days and 27 affected having a mean of 161 with a maximum range of 62 days, a difference of 16 days in the comparable average gestation time. Kalkus says, after much contact among horse-men in the goitrous field of the northwestern U. S. A., that "The majority of reports, however, indicate that the mares (producing goitrous colts) run overtime."

Welch (1917) of Montana may be quoted: "Many ranchers report that pregnant sows carry the pigs four to seven days longer than the average period, and a great many sows die at farrowing time." The data now available on the gestation period indicate that whereas a marked iodine deficiency, accompanied with goitrous offspring, may result in a somewhat prolonged period, a partial deficiency may promote a slightly earlier delivery.

#### EFFECT OF DEVELOPMENT ON NEW-BORN LAMBS

The birth weight, vigor, condition, and wool covering of the lambs (see Table VII) from the various groups were affected but little, if any, by the iodide feeding. Statistical studies of the data warrant this interpretation.

TABLE VII

BIRTH WEIGHT, VIGOR, CONDITION (DEGREE OF FATNESS), AND WOOL COVERING OF NEW-BORN LAMBS

(Average of Three Years—1926, 1927 and 1928)

Group No.	I (Check)	II (1/20 gr. KI)	III (1/5 gr. KI)	IV (4/5 gr. KI)
Lambs per pregnant ewe, average .....	1.78	1.78	1.64	1.83
Lamb weights, pounds average:				
Rams .....	9.35	9.30	9.70	9.11
Ewes .....	9.60	9.39	9.79	9.31
All. or both sexes.....	9.48 ± .20	9.34 ± .19	9.74 ± .20	9.23 ± .17
*Vigor %, average.....	82	78	76	82
*Condition %, average..	71	70	73	68
*Wool covering %, av..	81	81	81	78

\*Based on observations made according to a relative scale, 100% being considered as the maximum. Our judgment is that differences should exceed 8% to approach significance, inasmuch as these figures do not represent actual "measured" values, but are based on appraisals.

## THE MEASUREMENTS OF NEW-BORN LAMBS

The size of the new-born lambs, as determined by certain linear measurements, is given in Table VIII. Apparently, the iodide feeding had no effect on the body height, body length, leg length, heart or chest girth, and paunch or middle girth.

TABLE VIII

LAMBS—SIZE AT BIRTH  
(Average of three years—1926, 1927 and 1928)

Group No.	All Measurements in Inches			
	I (Check)	II (1/20 gr. KI)	III (1/5 gr. KI)	IV (4/5 gr. KI)
Withers (shoulder) height.....	14.17	14.13	14.10	14.06
Leg, fore, length.....	9.56	9.60	9.63	9.57
Shoulder top to Ischium, length.....	10.75	11.00	11.03	10.80
Heart or chest girth.....	14.82	14.90	14.83	14.86
Paunch or middle girth.....	15.21	15.18	15.06	15.31

## WEIGHT OF THYROID GLANDS AFFECTED BY IODINE FEEDING

Table IX gives pertinent data in regard to the weight of new-born lambs from which thyroids were taken, their sex, weight of thyroid in grams and ratio of thyroid to new-born lamb weights, together with other figures applicable to the problem in hand. This material is given by years as well as for the three years of investigation, averages being presented for the combined yearly periods.

A careful survey of Table IX shows quite clearly that the feeding of potassium iodide to the pregnant ewes affected quite markedly the weight of the thyroid glands of their resulting new-born lambs. The following deductions may be made:

1. In all three years the addition of small amounts of potassium iodide to the pregnant ewes' ration had a rather marked effect upon the average size of the thyroid glands of the new-born lambs, the weights being reduced in all instances.

2. In only one of the three years was there a break in the downward weight tendency of the thyroids. In 1927-28, Group II is somewhat out of line with the same group in the two preceding years, the average thyroid from three selected representative lambs being smaller than the glands secured from Groups III and IV receiving, respectively, four to sixteen times as much iodide. In this particular year the ewes presumably received more iodide in their basal ration because the glands are smaller than in the two preceding years, as may readily be seen

TABLE IX

WEIGHT OF THYROID OF NEW-BORN LAMBS DECREASED BY IODINE FEEDING  
Three Years Results, 1926, '27 and '28 on Thyroids Removed from Selected Representative Lambs

Group No	I—Chick	II—(1/20 Gr KI)	III—(1/5 Gr KI)	IV—(1/5 Gr KI)
<b>1925-1926</b>				
Lamb number.	2606	2372	1901	2196
Lamb weight pounds	11 0	8 5	10 0	8 5
Lambs in litter	2	2	2	2
Lamb, sex	Run	Lwe	Run	Lwe
Thyroid weight, grams	1 1616	0 8135	1 1023	0 6605
Thyroids weight, grams, average	1 2705	0 8101	0 7646	0 5983
<b>1926-1927</b>				
Lamb number	2656	2134	2162	2673
Lamb weight, pounds	8 9	9 1	8 8	9 5
Lambs in litter	2	3	2	2
Lamb, sex	Lwe	Run	Run	Run
Thyroids weight, grams	1 0083	1 0085	1 0110	0 6087
Thyroids weight, grams, average	1 1371	0 9147	0 8845	0 6364
<b>1927-1928</b>				
Lamb number.	2123	2306	2271	2131
Lamb weight pounds	7 3	9 3	10 0	8 6
Lambs in litter	2	2	2	2
Lamb, sex	Lwe	Run	Run	Lwe
Thyroids weight, grams	0 9840	0 6378	0 8553	0 8367
Thyroids weight, grams, average	1 0711	0 6793	0 7711	0 7121
<b>Three Years Combined</b>				
Lamb, weight pounds, average	9 52	9 31	8 90	8 36
Lambs in litter, average	2 00	2 22	2 00	2 11
Lambs, sex—				
Runs %	55 6	55 6	66 7	55 6
Lwes %	11 1	41 1	33 3	44 4
Thyroids, weight grams—				
Lowest	0 9840	0 6378	0 5518	0 4255
Highest	1 5607	1 0882	1 1023	0 8867
Average of all	1 1596	0 8214	0 8067	0 6526
Ratio of thyroid to lamb weight 1	3724	5111	5004	5811

by comparing the averages of the check lots. However, this particular variation is not of much consequence in affecting the final average results, altering them but little.

3. The average weight of the thyroids for all three years in Group I, from 9 lambs, was 1.1596 grams. This group received the basal ration without added iodide. Group II, receiving  $1/20$  of a grain of potassium iodide per ewe daily during the winter season, showed in the new-born lambs thyroids weighing 0.8214 gram, average. Group III, receiving  $1/5$  grain of potassium iodide, had thyroids weighing somewhat less, or 0.8067 gram, and Group IV, ingesting  $4/5$  of a grain of the superimposed iodine carrier, produced new-born lamb thyroids weighing, on the average, 0.6526 gram. The thyroids from Group IV, the heaviest iodide group, weighed 56 per cent as much as the thyroids of Group I, check.

4. The question arises as to what is a normal thyroid gland in a new-born lamb. The same question arises for other animals. We are proceeding on the assumption that the smaller the thyroid, within reasonable limits, the more normal and healthy it is, providing that the percentage of iodine contained therein is reasonably high and that the gland shows no pathological changes on microscopic examination. It may be well to emphasize likewise that the new-born lambs possessing these normal thyroids should not show adverse symptoms which may be attributable to a deranged metabolism on account of this gland. We shall see later how the size of the thyroids from the new-born lambs in our experiments correlate with the iodine content, both on the percentage basis and in actual quantity of iodine stored.

5. The thyroid glands of new-born lambs represented but a small proportion of the total weight of the lambs from which they were removed. On the ratio basis, taking the weight of the thyroid as 1, the smallest thyroid, relatively speaking, was found in Group IV in the first year of the experiments. Lamb No. 2631, weighing 10 pounds, possessed a body weighing 7970 times the thyroid contained. On the other hand, the largest proportionate thyroid was exhibited by lamb No. 2731 in Group I, receiving the basal ration without iodide addition, this lamb weighing 2814 times its thyroid. On the whole, the heaviest thyroids in proportion to body were in Group I, basal ration, these lambs weighing 3724 times their thyroids. In Group II,

receiving  $1/5$  of a grain per ewe daily, the new-born lambs showed a figure of 5141. The figure for Group III was 5004. And for Group IV, the heaviest iodide fed lot, the relative body weight was 5811:1. These findings are in harmony with the general trend of the data as regards thyroid weights.

6. The biometrical analysis of the data, covering the weight of the thyroids secured from the various groups, shows that the mean differences existing between Group I and II, III and IV were, respectively, 6.78, 6.48 and 10.26 times the probable error, which means that the chances are practically 100 per cent in favor of iodide feeding, as practiced in this series of experiments, decreasing the weight of the thyroids of the new-born. The difference between Groups I and IV stands out, being extraordinarily significant.

#### IODINE IN THYROIDS OF NEW-BORN LAMBS

The iodine found in the thyroids of new-born lambs, expressed in parts per million on both natural and air-dry basis, the actual iodine of the thyroids expressed in milligrams, and the ratio of the iodine, present in the thyroid, to the thyroid weight, fresh basis, are given in Table X. In this table the results of two years' study covering 1926 and 1927 lambings are given. The data on the third year will not be available for some time. Determinations covering the third year results as regards the iodine content of the thyroids as well as the iodine content of the bodies of the lambs which were removed for chemical analyses and other pertinent figures, including iodine analyses of the feeds, will be published in due course.

Professor J. A. Schulz and the author are co-operating on the chemical phases of these investigations, and to him is due the credit for the careful and painstaking analytical work done on the samples covering the three years of research under discussion.

In making the iodine determinations, Professor Schulz soon found that he was confronted with a number of perplexing problems in regard to methods of procedure. After several months' study he decided to use, essentially, the method of Kelly and Husband (1924), which is a modification of the third published method of Kendall (1920), with the exception that some of the procedures recommended by Kendall, but not considered neces-

TABLE X  
IODINE FOUND IN THE THYROID GLANDS OF THE NEW-BORN LAMBS  
Two Years' Results 1926-27

Group No.....	I—Check	II—(1/20 Gr. KI)	III—(1/5 Gr. KI)	IV—(4/5 Gr. KI)
1925-1926				
Lamb number.	2185	2372	1901	2496
Iodine in thyroids, parts per million—*	2370	2138	2397	2435
(a) Natural Basis.....	2212	2033	2192	2484
Average	571 2	1091 5	1328.1	1859 7
(b) Air-dry Basis..	500 7	1003 8	1061 6	854 4
Average	560 4	1383 8	1259 5	1391 1
Iodine in thyroids, mgs.	2511 7	1652 0	5591 1	6185 0
Average	2518 4	3413 3	1627 2	3891 4
	0 67	5438 7	5453 4	5683 0
	0 78	1 78	1 46	1 23
	0 70	1 17	0 50	0 51
			0 97	0 68
1926-1927				
Lamb number.	1098	1093	1099	1096
Iodine in thyroids, parts per million—	1100	1106	1101	1097
(a) Natural Basis.....	1103	1106	1107	1105
Average.....	805 4	1378 1	1529 8	2305 4
(b) Air-dry Basis..	430 0	2507 0	1671 3	2239 4
Average	620 5	1953 2	1476 8	1958 4
Iodine in thyroids, mgs.	3266 3	1589 0	6761 8	6960 9
Average	1915 5	7141 7	5602 4	5736 7
	2526 4	6166 6	5668 3	5839 2
	0 81	1 50	1 60	1 40
	0 57	2 53	1 50	0 95
	0 64	1 84	1 33	1 17
Two Years, Combined				
Iodine in thyroids, parts per million—				
(a) Natural Basis Average.....	590 4	1673 5	1363 1	1674.7
(b) Air-dry basis average.....	2527 4	5802 7	5560 8	5761.1
Iodine in thyroids, mgs. average	0 70	1 51	1 15	1.01
Ratio of iodine in thyroids to thyroid weight (fresh basis), average 1:.....	1693 7	597.5	733.6	597.1
Ratio of iodine in thyroids to lamb weight, average 1'.....	6,307,359	3,071,748	3,670,931	3,469,748

\*To convert parts per million to percentage basis move the decimal point four places to left. Examples: 560 1 p. p. m. equals 0.05601%; or 1383.8 p. m. equals 0.13838%.

sary by Kelly and Husband, were adopted. The method used by Schulz was carefully checked on known iodine carrying samples before putting it into execution.

Deductions for the data given in Table X are presented herewith:

1. The addition of iodide to the basal ration fed the pregnant ewes resulted in an increase in the proportion of iodine in the thyroid gland of the new-born offspring. We have expressed the iodine in parts per million in order to make the figures more quickly and easily intelligible. The new-born lambs from the basal group, I, appear to have been on the border of iodine deficiency. According to Marine (1924) the iodine content of the thyroid gland, when maintained above 0.1 per cent or 1000 p. p. m., protects against goiter. One of the lambs in Group I had only 430 p. p. m. of iodine, and the average of all was only 590.

The indications are that a near-maximum content of iodine, 1,674 p. p. m., was secured by the smallest dosage, or by 1/20 of a grain of KI daily per ewe. When the dosage was increased to 1/5 of a grain the p. p. m. of iodine was lowered to 1363. A further increase of 4/5 of a grain altered the iodine content but little, 1675 p. p. m. While the larger administration of iodide decreased the size of the thyroidal structures, this atrophic effect was apparently not due to increased iodine storage. It is possible that 1/20 of a grain per ewe daily was sufficient to supply all nutritional needs; at least it so appears.

2. The maximum storage of iodine, 1.51 milligrams per gland of the new-born, was attained when the mothers received 1/20 of a grain KI per head daily, whereas the average thyroid from the lambs of Group I, on the basal ration, carried only 0.70 mgm. of iodine, or less than half as much. Since these are averages based upon two years' results, they appear quite dependable. On the other hand, the increase of the iodide allowance to 1/5 of a grain actually brought about a decrease in the amount of iodine in the gland to 1.15 mgs. And a still further increase of the iodide fed to 4/5 of a grain induced an even greater decrease, to 1.01 mgs. In consideration of the fact that the results covering the storage of iodine in the thyroid are consistent for

the two years, it would seem that the height of iodine storage in this endocrine is reached at comparatively low levels of iodine ingestion. It may be that the thyroids are relieved, in part, of their duty or duties when iodine in excess of so-called normal requirements is given.

Can it be possible that in the presence of a moderate excess of iodine in the somatic tissues that less metabolism is required on the part of the thyroid? In the absence of sufficient iodine in the tissues (or certain tissue) may it be that a certain substance (or substances) is (or are) formed which overtax the thyroid, or cause it to become toxic in itself, and thus produce hyperplasia, followed with that more serious pathological development, exophthalmic goiter? Anyhow, it is suggestive that the thyroids may decrease in size from 100 units to less than 81 units weight (compare Groups II and IV), whereas at the same time the iodine contained decreases at an even greater rate, from 1.51 to 1.01 mgm., or from 100 units to less than 67 units weight. It may be argued, of course, that the number of observations are not sufficient to warrant much philosophizing along these lines, and this hypothesis is granted. We hope to have more to contribute on these hypothetical problems as the years unfold.

3. The ratio of the iodine in the thyroid to the weight of this endocrine was as 1:1694, in round numbers, in the average lamb of Group I. The proportion of iodine was increased, 1:598, when 1/20 of a grain of iodide was fed. The ratio was 1:734 when 1/5 grain was allowed, and 1:597 when 4/5 grain was administered. The ratio of iodine to the air-dry thyroid weight shows a similar relationship, the proportion of air-dried thyroidal material for Groups I, II, III and IV to iodine being respectively, 396, 172, 180 and 174:1.

4. Parenthetically, it is well to call attention to the fact that Ames, from the domestic animal standpoint, is in a semi-goitrous region. In our herds and flocks we have observed visible external goiter in aggravated form in five out of the fifteen years since 1913. In our breeding sheep flocks on the college farms serious trouble has been experienced with goitrous newborn lambs. Much depends upon the rations fed and general



environment, because a flock on one portion of the farm may show goiters at lambing time, whereas a contemporary flock in a different area, housed in another barn, do not. When iodide feeding as a preventive measure has been resorted to, however, goiter has never shown its head in the new-born.

5. If the thyroids are enlarged sufficiently not to function adequately, it can hardly be expected that such glands would be suitable for therapeutic use. One of the reasons why summer gathered glands are preferred by some practitioners is very likely due to the higher iodine content, as well as the more normal functioning status of such glands. It is during the pasturage season that sheep, for instance, increase their iodine stores, and hence it is during this period that the glands are reduced in size. At least one would so judge, if the evidence in this paper is sufficient to prove the basal principle upon which this deduction is based.

6. The relationship existing between the weight of thyroidal iodine and the new-born lamb, as given in the lowest horizontal column of Table X, is of interest. The non-iodide fed lambs carried 1 part of thyroidal iodine per 6,037,359 parts of lamb weight; on the other hand, the administration of  $1/20$  of a grain KI per pregnant ewe daily caused a higher concentration, or 1 part iodine per 3,071,738 parts lamb. By carrying the iodide dosages at a higher level,  $1/5$  and  $4/5$  grain, we lessen the iodine proportions to, respectively, 1 part of iodine per 3,670,934 and per 3,469,748 parts lamb. How will larger intakes of iodide fed the pregnant ewe affect these relationships? When we have available the iodine figures in the lambs' bodies, excluding thyroids, we shall be in a somewhat better position to discuss this question of the quantitative relationship of thyroidal iodine and lamb weight.

#### EFFECT OF IODIDE FEEDING ON WOOL GROWTH

The fleece or "unscoured" wool yields are given in Table XI. The results are close, but the data suggests, possibly, a slightly favorable influence. Biometrical data covering the probable error of the differences show that the chances of iodide

feeding increasing the fleece yield over the check group, not fed iodide in addition to the basal ration, are respectively 72, 86 and 63 out of 100. The combined groups, II, III and IV, fed iodide show 79 chances out of 100 in favor of an increased yield on repetition of this series of experiments. The coefficients of variation in fleece yields for the various groups were quite similar, indicating close uniformity of fleece yields within the groups as well as among the groups. It is thought that the slight tendency to increased gross yield may be due to an augmentation of the skin secretions, weighed as "grease" in the wool fleeces.

While it is true that wool-less new-born lambs are sometimes observed in cases of iodine deficiency, yet this influence may be entirely a pre-natal one, one not affecting the wool growth on growing or mature sheep. The causal agent which initiates a process may be inessential thereafter.

TABLE XI  
FLEECE YIELDS OF THE EWES  
(Average of Three Years)

Group No.	I	II	III	IV	Iodide Fed Groups II, III, IV Combined 90
No. of fleeces...	30	30	30	30	90
Weight, lbs. av.	8.02 ± .13	8.17 ± .11	8.35 ± .17	8.12 ± .17	8.21 ± .09

#### SUMMARY

Iodine plays an essential role in the thyroid and bodily metabolism of domestic animals. A brief survey of important literature showing the significance of iodine in domestic animal physiology and economy with its relationship to the thyroid gland function, pathology, etc., and body development, is presented along with some philosophy, observations, and interpretations made by us.

Potassium iodide fed to swine in a semi-deficient "iodine" region, Central Iowa, resulted in greater growth (weight and dimensional) and in feed economy, even though no observable gross symptoms of any goitrous condition were noted.

The administration of iodine as potassium iodide to breeding sheep prevented goiter in the new-born lambs, but its allow-

ance in excessive dosages had apparently a deleterious influence, particularly in lessening resistance against hemorrhagic septicaemia. Certain hypothetical questions covering causative factors are raised. The heavy administration of iodide to ewes caused their milk to be high in iodine for a brief period.

Increasing dosages of iodide, from none to  $4/5$  grain per ewe daily, decreased the size of the thyroids in the new-born lambs and increased the percentage of iodine in the glands. The milligrams of iodine per lamb thyroid was augmented by a small ingestion of iodide,  $1/20$  grain KI, but decreased thereafter by larger dosages,  $1/5$  and  $4/5$  grain KI. The thyroidal iodine in the lambs at birth figured on the weight basis as 1 part to 6,037,359 (check group, no iodide); to 3,071,738 ( $1/20$  grain KI dosage); to 3,670,934 ( $1/5$  grain KI); to 3,469,748 parts ( $4/5$  grain KI). Proportionately speaking, the iodine in the thyroids represent but an infinitesimal portion of the total weight of the new-born.

The correlation between the thyroid size and its iodine content, per cent and actual, of new-born lambs is altered by the quantitative allowance of KI to the ewes.

Data are presented showing the effect of the administration of iodide to sheep on growth, feed economy, gestation period, wool (fleece) growth, character of the offspring, and other items of importance.

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# STUDIES OF THE ENDOCRINE GLANDS

## IV. The Male and Female Gonads

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In a series of papers from this institution, a general method for the diagnosis of endocrine disorders has been described in detail (1) and the results obtained from its application to pituitary and thyroid malfunctions presented (2) (3).

This paper summarizes our results with cases showing aberrations of the primary sexual organs, the testicles and ovaries. In presenting this material, the authors earnestly desire to avoid the controversial element which has operated greatly to enlarge if not enrich the literature. To that end only the observed facts will be presented, with such conclusions as are directly warranted. Certain of our findings are distinctly unorthodox in relation to more or less generally accepted theory, and it is felt that the actual data will be more significant if unembellished with a mass of supporting polemic.

The enormous social and economic import of the exocrine functions of these glands, coupled with the usual assumption of interdependence upon the internal secretory activities, has inevitably colored thought and influenced trends of study. From earliest record, speculation has endowed the sex organs with a multitude of attributes basic to the whole scheme of existence. It remained for Brown Séquard to render concrete the surmises of Berthold—or even Bordeu, to make the happy alliteration complete—and realize an acceptable recrudescence of the best traditions of Egyptian mysticism and medieval alchemy. The influence of sex upon physical and mental habitus has long been recognized. Emasculation practised in man in conformity with various religious beliefs and in the domestic animals for economic reasons, derives from a remote antiquity. The striking outward

differences that pertain to sex in the higher forms of life and their modification by ablation of the sex glands, must early have been recognized, and as a result castration was practised to confirm certain qualities that unchecked maturation would have destroyed. Sex and reproduction are not identical, though the latter depends upon the former in the more evolved forms of life. Sex implies phylogenetic differentiation; reproduction, the fusion of the differentiated parts. It is the external manifestations which are the prime factor in reproduction which is, after all, the one essential. But conservative interpretation of experimental evidence regards a concomitant endocrine function as one essential for the proper development of those portions in which the outward capacities have their origin. Other equally potent endocrine agencies must likewise be admitted if current belief as to the genesis of *pubertas praecox* and kindred developmental anomalies be accepted. The more expansive—and less critical—views that merge in the function of the sex organs, the gamut of physical and mental characteristics of man, do not require discussion. The due sequence of the stadia of development leading first to maturity and later to the recessions incident to the decline of reproductive power are intrinsic, seemingly, in the proper functional adjustments, not only of the gonads themselves but of a number of other centers of endocrine activity. The genital arrests of pituitary and thyroid failure do not, *a priori*, connote a simultaneous loss of internal secretory function on the part of the testicle or the ovary. Ablation of the gland with the removal of those cells which are usually assumed to be the seat of endocrine activity, also robs the organism of those in which the external function is engendered. The data from incomplete suppressions such as the subjects of x-ray sterilization, vasectomies and salpingectomies, and from cryptorchids, are inconclusive, since the sterilities may be no more than mechanical interferences. The degenerative changes apprehensible by careful histological examination do not exclude rigorously all traces of the parts of exocrine function. When one realizes how fractional residua are capable of maintaining function, it would seem wise to maintain a genial scepticism toward the comprehensive generalizations based on partial experiments. Transplantation studies suffer from the same objection as those involving complete ablation, since all portions of the gland

participate in the experiment. While striking results are obtained, the lower animal species seems to play the predominant part in the phenomena evoked, the sexes being unequally and not uniformly influenced in those groups where changes are demonstrable. The use of organ extracts offers perhaps the most definite potentiality, but here again the presence of extraneous active material on the one hand, or the destruction of the active principle during extraction on the other, places obstacles in the way of unqualified success. That these are in fair way to be overcome, would seem to be certain from the success that has attended the studies with others of the endocrine group. But even here a temperate conservatism must be observed. Striking as have been the results with rats and mice by the use of "follicular hormone" the alleged excitation of oestrus in the spayed female with extracts of testicles and other foreign substances raises a natural question as to the specific character of the phenomenon. A detailed recountal of the difficulties attending the solution of these several problems lies outside the scope of the present thesis.

To summarize the facts pertinent to this discussion, it may be said that the primary sex organs have respective exocrine functions from which the reproduction of the species derives. Further, there is evidence of an internal secretory function of the primary sex organs, well established in the female and probable in the male, at least in the years preceding maturity. Man, generically speaking, passes through three well defined periods of existence,\* determined by the power of reproduction. In the female there is possibly a further subdivision intrinsic in the oestrous cycle and the immediate results of reproduction as manifested by pregnancy and lactation. These are, however, but incidental to her period of fertility, and merge in it in a general classification. During the first of these, the period of growth, many processes are going on in the body in which an endocrine activity of the gonads may or may not be involved. From the results of castration in this period† there would seem to be abundant evidence that such loss to the growing organism induces gross somatic changes of an unmistakable character.

\*Lipschütz (4) denies this.

†The observations are based wholly on the male. The results of prepubertal castration in females is recorded only by Roberts [cited by Marshall (5)], and but little credence is attached to his reports.

Castration in adult years of both males and females is a common surgical procedure. Inversion of outward sex habitus is the common report although the somatic changes are less striking, as growth possibilities, at least of the bony structures, are definitely restricted. Castration in advanced years is attended by less striking changes though the development of marked hirsuties in aged females is, at times, referred to as a manifestation of a "physiological castration" implying suppression of ovarian function as an incident of the degenerative changes of senility.

Fundamentally, the sexes are sharply differentiated,\* although many cases of apparently indeterminate sex are recorded in the literature and these must represent but a small part of existing cases. The multiplicity of genital anomalies producing this end result is not to be wondered at when embryonal relationships are considered. For example, in the series of nearly two thousand cases from which the present group are excerpted, there were three complete visceral inverters, a more comprehensive developmental aberration than hypospadias or analogous conditions which contribute so large a proportion of the pseudohermaphrodites. In dealing with the gonads then, it is necessary to treat them separately, as organically and functionally they are completely differentiated structures. Furthermore, the ovary is seemingly concerned, directly or indirectly, with a large number of important functions incident to reproduction, which find no correlative activities in the male. Finally, in the corpus luteum the ovary develops transiently a new potential source of endocrine activity seemingly independent of the other portions of the gland.

Needless to say, from any center in which a wide variety of functions find their origin, changes may occur which will influ-

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\*In Neugebauer's (6) exhaustive compilation but five cases of true hermaphroditism are recorded [see Garre (7), Simon (8), Pick (9), v. Salen (10), Schickle (11), and Unger (12)] and in each of these only a single ovotestis was demonstrated, the other being unitary organ. The few other alleged cases recorded are lacking in positive demonstration. More recently, Neumann (12a) has compiled a number of cases from the more recent literature. Of the ten where ample description was available to him, he regards four at least as doubtful. An eleventh [Berblinger's (b) case] was described only in a note and cannot be passed upon. Of the six which he accepts, only one (Robert Meyer) (c) shows bilateral ovotestes. He cites an additional ten from foreign literature not to him available, of which two are doubtfully authentic, two [Briau, Lacassagne & Lagouette (d), Masson (e)] are bilateral ovotestes, and the remainder range from Burden's (f) amply provided individual with an ovary and a testicle on each side, to the more modest equipment of Baldwin's (g) patient with a left ovary and right testicle.



ence some but not all of the several activities. To illustrate, the functional level of activity of the ovary during pregnancy remains a matter of speculation. By many, an overactivity is inferred, while others see a period of quiescence with lessened functional level. Thus we may expect widely divergent pictures in the three phases of life as conditioned by reproductive activity. That the immature child should offer the same evidences as the adult is possible but not probable. Even though we concede—as is not usually done—that the reproductive mechanism is entirely independent of the normal endocrine activities of the gland, the establishment of new functions in one set of cells would seemingly influence, even though by indirection, the behavior of other cells immediately adjacent to them. The problem then is admittedly intricate, and only by limiting the variables so far as one may is it possible to arrive even at a first approximation.

The cases reported here, with but non-significant exception, are adults. Work with children in the prepubertal period calls for other standards, at present imperfectly defined, and in some cases even for other methods of approach. All of the women here reported had established the catamenia, and but two of the males were immature. The inclusion of these, as will be shown later, has larger measure of warrant than would be the case with the opposite sex. Post-menopausal cases appear among the women, as the differences in this stadium are of degree rather than of kind.

Another point requiring amplification is the designation of all of the cases as "hypofunctional." The literature contains frequent reference to a hypergonad state. We have never been privileged to see such a condition. Unquestioned hypofunction is produced by castration, and the study of a group of such cases defines a clinical and laboratory picture of fairly clear-cut outline. The antithesis of this picture we have never seen. Pubertas praecox cannot be regarded as a hypergonad state, particularly if we accept the alleged influence of other endocrine entities as causative. It becomes, under these conditions, an interesting but resultant developmental anomaly to be contrasted with the arrests engendered by pituitary and thyroid failure. A libido in excess of the usual conventional standard is certainly no warrant for the assumption of a hypergenital con-

dition. Even conventional standards vary and some allowance must always be made for the personal factor operative in normality. Further, it is well known that libido persists, sometimes for long periods, in individuals who have lost the primary sex organs in adult years. If libido be the criterion of gonad activity, we have in this fact a most uncompromising contradiction. The fact is that the assignment of restrictive limits to the normality of the sex urge is on a parity with other ex cathedra utterances unhampered by a paucity of basic fact. And above all, the fact remains that in a considerable group of individuals referred for study as hypergonad cases, not one has even suggested a clinical and laboratory picture the opposite of that produced by castration.

TABLE I  
PHYSICAL MEASUREMENTS

Observation		Male	Female	Remarks
Number of Cases		11	189	Total=200
Distribution	%	5.5	94.5	
Age (yrs.)	High	77	68	
	Low	10	14	
	Average	34	34	
Height (cm.)	High	175	175	
	Low	146	140.5	
	Average	166	161	
Sitting Height (cm.)	High	93	94	
	Low	75	75.5	
	Average	88	86	
Sitting Height Index		0.530	0.534	
Chest (cm.)	High	99	121	
	Low	79	60	
	Average	87	77	
Trunk Chest Index		1.010	1.117	
Weight (kgm.)	High	80.7	124.0	
	Low	50.5	35.8	
	Average	64.4	60.4	
Area (sq. m.)	Average	1.72	1.64	
Lung Volume (c.c.)	High	4940	4000	
	Low	1800	930	
	Average	3710	2600	

Obviously, as no "hyper" state can be defined, the intermediate zone of dysfunction becomes equally impossible to designate. True, all disturbances of the endocrine glands might be termed dysfunctions, as is from time to time suggested. But with such clear-cut and sharply differentiated entities as are presented by the thyroid and pituitary for example, it bespeaks a meticulous rather than a scientific caution to insist on a carefully non-descriptive classification.

As all of our cases accord in kind, though not in degree, with the results produced by complete ablation of the sex glands, we feel warranted in designating them as hypofunctional in character.

With these introductory remarks, presented to define a position and not to excite acrimony, we may turn to the consideration of the data of the several observations. Following the sequence of the earlier papers, we may first take up the physical measurements and certain related statistics. These have been collected in Table I.

The sex disproportion is striking, and as a statistic may be misleading. Pathological changes in the testicles are seemingly of less frequent occurrence than in the ovary. Our figures probably represent a trend rather than a definition. There is a wide span of age, but as has already been noted, the prepubertal element is practically absent.

TABLE I-a  
AGE DISTRIBUTION

Years	%
11-20 .....	13.5
21-30 .....	37.5
31-40 .....	22
41-50 .....	18
51-60 .....	6
61-70 .....	3

Only six of the women were less than eighteen, (two at fourteen and sixteen, one each at fifteen and seventeen) and, as before stated, menstruation had been established in every case in this group. This exocrine sign of maturity is conventional but is probably the best criterion to adopt. The absence of the male, castrated in prepubertal years, eliminates the abnormally tall adult eunuch, and the average height recorded compares well with usual normal standards. The women are equally not remarkable.

Sitting height indices show no departure from the normal, and the several other measurements might easily represent those of a group of healthy average individuals. The authors recognize that the elimination of the prepubertal case exercises an influence, but were they included, for proper presentation they would fall in a separate category and so be without influence

on the data as presented. The arbitrary inclusion of a group of children with the adults would synthesize an artefactual relationship that would be meaningless.

While the raw data of actual measurement have true significance, relationships of the individual to some established standard indicate a trend more strikingly. The use of the Dreyer and West standards, under limits already defined (13), offers a basis for one such comparison.

TABLE II  
"VITAL CAPACITY" OBSERVATIONS

Observation		Male	Female
Weight .....	High	+34%	+107%
	Low	-15%	-41%
	+Average	+18%	+22%
	%	60	51
	-Average	-10%	-12%
	%	40	49
Chest .....	Net Average	+7%	+5%
	High	+19%	+66%
	Low	-2%	-19%
	+Average	+9%	+12%
	%	60	47
	-Average	-2%	-7%
Lung Volume.....	%	40	53
	Net Average	+4%	+2%
	High	+14%	+23%
	Low	-58%	-67%
	+Average	+9%	+6%
	%	40	11
	-Average	-17%	-22%
	%	60	89
	Net Average	-7%	-19%

The few males vary within far more restricted limits than do the females. This may result from the paucity of observations in the male series. Certainly there is not apparent that tendency to obesity that is considered a cardinal evidence of gonad failure. Tandler and Grosz (14) recognize two types of eunuch, the "tall" and the "fat," and consider that these repeat in the eunuchoid group. In this series there is obviously not enough obesity to conform to the one, and the heights recorded in Table I eliminate the other. In other words, neither by castration nor by destruction of gland function by disease in adult years, is the typical habitus of the prepubertal castrate necessarily realized. Numerous other records show that in a percentage of cases they do conform, but the observation may

well be a result of extraneous causes. Certainly in this carefully studied group there is no defined tendency toward a typical obesity. On the other hand, the majority of the cases fell within the limits of a relative normality. The chest repeats the weight comparisons, as naturally could be predicted. The lung volume comparisons show a definite sex difference. The men are compared to Dreyer's standard "A," comprising athletes, soldiers, sailors, and active outdoor workers. The male gonad failures average but 7 per cent below this rather rigid standard, though the constituent members were not engaged in the active pursuits of Dreyer's classification. The women, on the other hand, are compared with Dreyer's female standard "B," and even under these more elastic conditions, fall, on the average, 19 per cent below prediction. Any impairment of normal vigor tends to be reflected moderately in this measurement. The striking feature is the relatively normal performance of the men.

The data from certain urine examinations are presented in Table III.

TABLE III  
URINE MEASUREMENTS

Observation	Unit	Male	Female
Volume ..... High	c.c.	1440	3000
Low	c.c.	460	230
Average	c.c.	1120	1130
Spec. Grav..... High		1.032	1.035
Low		1.011	1.005
Average		1.021	1.019
Albumin .....	%	9	27
Casts .....	%	9	19
Sugar .....	%	0	23
"Urobilinogen" .....	%	0	0
Amylase Index .....		18	16
Salol .....	min.	75	81
Urea Curve..... Normal	%	60	54
Delayed	%	0	24
Progressive	%	0	6
Low	%	40	16
Phenol Sulphone Phthalein			
2 hour Elim..... Av.	%	51	55

The sex differences here in the main are slight. A possible exception is the seemingly greater incidence of renal disturbance in the female group, an expression conceivably of nutritive disturbance of the kidney. The one salient difference is the appearance of glycosuria in nearly one-fourth of the female cases,

it being totally absent from the other group. This will be discussed at length in the section devoted to carbohydrate tolerance.

In spite of the evidences of kidney disturbance, the phthalein test shows a slightly higher value for the women. The difference is scarcely significant. To summarize the data of this table, the men show a uniform normality that is somewhat striking, while the chief aberrations of the female group lie in certain evidences of a kidney disorder, which may well be referable to a disturbance of nutrition and in a frequent slight glycosuria. The nitrogen partition data given in Table IV but re-

TABLE IV  
NITROGEN PARTITION

Observation	Unit	Male	Female
Total Nitrogen.....Av.	Gms.	11.34	8.46
Urea Nitrogen.....Av.	%	83.6	80.3
Uric Acid Nitrogen.....Av.	%	1.9	2.1
Ammonia Nitrogen.....Av.	%	2.8	4.0
Creatinin Nitrogen.....Av.	%	4.3	4.5
Residual Nitrogen.....Av.	%	7.4	9.1
% = or > 9.0%.....	%	36	48

peat the first indications. High residual nitrogen has been previously shown to be associated with metabolic disturbance of endocrine and non-endocrine regulators. In the present case, the percentage of male cases exceeding the conventional limit of 9 per cent is less than in a series of non-endocrine disorders. The female group equates in frequency with the pituitary and the thyroid groups, falling short only of the adrenal, with which superimposed nephritis is almost concomitant. Further, the male average is well below, the female slightly above the limiting value that our experience has established. That hypogonadism in the female engenders certain metabolic disturbances, is the only conclusion that one may draw. The inevitable corollary is that the testicle gives no evidence in these studies of a similar influence.

The blood chemistry naturally equates with the urine findings, being the source from which the latter originates. Certain of the results are grouped in Table V.

At first sight it would seem as if the blood findings of the male presented an opposite picture from those of the urine. All the nitrogenous constituents are higher, and in the case of the

TABLE V  
BLOOD CHEMISTRY (AND SEROLOGY)

Observation	Unit	Male <sup>(1)</sup>	Female	
Non-Protein Nitrogen.....Average	mgm.	36	31	
% > 35 mgm.....	%	36	14	
Urea Nitrogen.....Average	mgm.	16	14	
% > 17 mgm.....	%	27	10	
Uric Acid.....Average	mgm.	3.6	3.2	
Net (%) > 4.0 mgm.....	%	11	8	Total Average = 8%
Creatinin.....Average	mgm.	1.7	1.5	
Residual Nitrogen.....Average	mgm.	13.1	15.3	
Sugar.....Average	mgm.	95	96	
% > 120 mgm.....	%	0	3	
% < 80 mgm.....	%	0	6	
+ Wassermann.....	%	0	2	
	number	0	0 <sup>(2)</sup>	
	number	0	0	
	number	0	0	

(1) While the figures for blood nitrogen are influenced by the inclusion of the two nephritics, the upward tendency is still manifest if their data are omitted.

(2) All demonstrated cases of gout and nephritis have been deleted.

(3) Test not applied to two patients with positive wassermann.

non-protein nitrogen, exceed slightly the usual normal limit. The inclusion of two nephritics plays some part, but there is an upward tendency even when their data are omitted. It may be remembered that the average nitrogen elimination of the male group was one-third greater than that for the female moiety. This too would exercise some influence but not enough to account for the disparity recorded. The really significant datum is the residual nitrogen fraction, and here a definite increase is unquestionably manifest. Omitting the nephritics, it still falls slightly above the conventional limits ( $15 \pm 2$  mgm.) of the normal. In this observation we find the first real evidence of a metabolic disturbance dependent upon deranged testicular function. Blood sugar levels exhibit no sex difference, and the averages are not only rigorously normal, but the composing members almost equally so. All of the males showed entirely normal blood sugar levels which, coupled with the complete absence of glycosuria in the cases of this group, would imply an absence of testicular influence on the carbohydrate metabolism. The few females showing values above 120 mgm. reached only a maximum observed level of 125 mgm. That an emotional response may have conditioned some of the higher figures, is highly probable. Similarly, in the group falling below 80 mgm., the inferior limit was at 75, and the average for the group, 77 mgm., a decrease of very modest proportions. The significant point in this connection is the association of a strictly normal blood sugar with the observation earlier recorded of glycosuria in nearly one-

fourth of the female cases. This will be touched upon in the later discussion on carbohydrate metabolism. Before leaving these data, attention is called to the normal level of the blood uric acid throughout the series, a point of significance in the differential diagnosis of endocrine disorders, as has been shown previously. It will be noted that two positive Wassermans (1 per cent) are reported in the series. Both of these subjects were surgical castrates, and the luetic element could be regarded only as a non-endocrine disease superimposed on an established hypogonadism. On this ground, their inclusion was felt to be warrantable. Incidentally, the findings in one case agreed exactly with those of the uncomplicated castrates, and in the other, only the sugar tolerance departed from the usual finding.

The blood morphology of the two groups offers certain points of interest.

TABLE VI  
BLOOD MORPHOLOGY

Observation	Unit	Male	Female
Haemoglobin .....Av.	%	90	88
Erythrocytes .....Av.	10 <sup>6</sup>	5.12	4.84
Color Index.....		0.88	0.91
Leucocytes .....Ave.	10 <sup>3</sup>	8.0	7.6
P. M. N. Neutrophiles.....Av.	%	58	57
% = or > 75%.....	%	9	4
Lymphocytes .....Av.	%	35	35
% = or > 33%.....	%	55	56
Eosinophiles .....Av.	%	2	2
Net (1) % = or > 3%.....	%	27	21
Monocytes .....Av.	%	5	6

(1) Cases have been deleted in which a non-endocrine cause of eosinophilia has been demonstrated.

The general examination reflects the normal sex differences, the absolute values being substantially normal throughout. The differential count shows, on the one hand, no sex difference, and on the other, that slight upward tendency to the lymphocyte fraction which has already been noted in connection both with other endocrine malfunctions and also a group of non-endocrine disorders. Borchardt (15) and Sauer (16) have also both commented on a general incidence of lymphocytosis in all endocrine disorders. Antonelli (17) observed that castration in dogs lowered haemoglobin, both red and white cells and was



coupled with lymphocytosis; the latter observation was confirmed by Hermann (18) after ovariectomy. Naegeli (19) regards the characteristic picture of chlorosis as dependent on ovarian failure. He was, however, unable to determine a chlorosis in a ten-year observation of a young woman castrated at seventeen to correct a "moral insanity." The ovaries were normal and the patient had matured before the operation, however. Guggenheim (20) reports lymphocytosis in eunuchoids, and Falta (21) recognizes a constant increase of monocytes. A tendency toward a slight eosinophilia is evident, although the average value falls within normal limits. Generally speaking, the blood picture presents nothing remarkable.

The respiratory metabolism, with its concomitant measurements, has claimed a somewhat larger measure of attention.

TABLE VII  
RESPIRATORY METABOLISM

Basal Metabolism— Deviation	Observation	Unit	Male	Female
	High	%	-1	+9 <sup>(1)</sup>
	Low	%	-20	-25
	+ Average	%	-	+4 <sup>(1)</sup>
	%	%	0	7 <sup>(1)</sup>
	- Average	%	-11	-13
	%	%	100	93
% above +10%		%	0	0
% between +10% and -9%		%	36	36
% = or below -10%		%	64	64
Blood Pressure	Systolic Average	mm	109	111 <sup>(1)</sup>
	% < 110 mm	%	73	62
	Diastolic Average	mm	65	69 <sup>(1)</sup>
	% < 65 mm	%	73	15
Pulse Rate	Average	per min	67	75 <sup>(1)</sup>
% = or < 70		%	73	31
Respiration Rate	Average	per min	15	16
% = or < 10		%	9	9
Temperature		deg F	98.0	98.1
Alveolar CO <sub>2</sub>	Average	mm	41	35
% > 35 mm		%	91	60
% = or < 30 mm		%	0	26

(1) The positive basal rates in this group are somewhat questionable, as the nervous element cannot be wholly eliminated. Certain other observations are likewise influenced by this factor. The determinations were made with the utmost care and the data may be regarded as representative for this type of case.

Only the effects of castration need be considered in detail. The ignorance of functional level during pregnancy, indicated by the contrary opinions that have been offered, eliminates this state from present consideration.\* The influence of menstrea-

\*One of us (22) has shown in an extended study that the average basal rate shows a progressive increase during this condition, exceeding that determined by increased body weight (from -8 to +8 per cent during the last thirty six weeks). Sandiford's (23) explanation that this increase represents the foetal surface contribution, invokes uncertain extrapolation, and is based on the study of a single case.

tion is likewise not pertinent, as it interjects one more element of variation which is not yet clearly related to the internal secretory activities of the gland. The general, but by no means universal, impression seems to be that there is a slight increase during the period. From another standpoint, there is no ground, *a priori*, for the assumption that the menopause should condition any change. The cessation of the exocrine function of the gland certainly does not prove a like inhibition of internal secretion. The applicability of the Harris-Benedict (24) equation for women, and the Aub-duBois (25) generalization, have been verified by us with a number of normal women well past the menopause.\* Turning to the results of castration, Zuntz's (26) reports can at once be discarded, since his patients were not in a basal state. Curatulo and Tarulli (27), Loewy and Richter (28), Murlin and Bailey (29), Kojima (30), Angolitti (31), Heymans (32), Korenchevskii (33), and Tsubura (34), all report animal experiments in which castration produced a lowering of the basal rate in moderate degree. Lüthje (35) observed no change but his animals were not basal. Bertschi (36) with Asher could find no difference in castrated animals of either sex. Gräfe (37) in 1923 concludes that only exceptionally will ablation or loss of function produce a lowering of the basal rate, an opinion in which duBois (38) seemingly concurs. Plaut and Timm (39) report a temporary lowering, but as their "castration" is produced by x-ray sterilization, the observations hardly equate with the foregoing records, nor do they seem to warrant the rather comprehensive generalizations which the authors offer. Critical analysis of their results would lead to conclusions quite other than those presented. To summarize, it may be said that existing evidence is contradictory and opinion divided.

The data of our own series would seem to demonstrate a slight but unmistakable depression of the respiratory metabolism. In the group of castrated women without other demonstrable complication, the values range from  $-7$  per cent to  $-23$  per cent, the average of the group being  $-14$  per cent, or substantially that of the entire series. The data of the com-

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\*Twenty women ranging from fifty to seventy-seven, with an average of sixty years, showed basal rates from  $-1$  to  $+12$  per cent, with an average of  $+5$ . A similar group of 29, the ages of whom lay between 50 and 78, with an average of 57, exhibited rates ranging from  $-1$  to  $-12$ , the average in this case being  $-5$ . Unpublished data.—A. W. R.

plementary male group show an average of only —8 per cent, less than that of the complete male series. The limited number of the male cases, however, precludes a generalization which is warranted in the female series. A further point which bears directly on the observed magnitudes is implied in the foot note of the table. It has been our experience that the women presenting gonad failure exhibit, in a peculiar and marked degree, a quality of nervous tension and irritability (v. i.). Basal tests with them are far less satisfactory than with any other type of endocrine failure. An inability to remain absolutely quiet for even the period of a basal rate determination is frequently remarked, and this destroys the absolute basality of the measurements. While all observed basal rates determined by open or closed circuit methods are to be regarded as maxima\*, in our opinion, the nervous instability of the female hypogonad is more likely to assume detrimental magnitudes than in any other condition studied. It must be remembered further that this source of error operates uniformly irrespective of the method used. Benedict and Benedict (40) have called attention to the serious error which may result from even minor muscular activity, and our own experience amply confirms their conclusion. The same disturbing element is operative in blood pressure and pulse rate measurements. These effects are too well known to require comment. Loss of function of the gonads would seem to depress blood pressure in both sexes, and possibly the pulse rate in the male. Averages are conceivably misleading, as has already been pointed out, and the relatively large number of female hypogonads exhibiting hypotension of a significant degree, is concealed in this necessary form of presentation. As a matter of fact, 62 per cent of the female series showed systolic blood pressures below 110 mm., and many of these were below 100. The definite lowering of the male blood pressure is seemingly a tangible evidence of an existing influence. Respiration rates and body temperatures show no departure from the normal in either sex.

In the last datum of the table, the alveolar carbon dioxide, a definite sex difference is found. Tensions in the male are entirely normal; in the female, on the other hand, there is a marked

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\*In such measurements all of the potential sources of error—barring only the gross mistake of spent soda lime or faulty gas analysis—operate to increase apparent oxygen consumption.

downward tendency which, in one-fourth of the series, produces levels ordinarily associated with acidosis. A like depression of  $\text{CO}_2$  tensions in pregnancy was first recorded by Hasselbalch (41) and his findings were confirmed in detail by one of us (42). A possible import to this observation will be discussed later.

The last observation of the series here recorded deals with the carbohydrate tolerance. Prior to the establishment by one of us (43) of an intrinsic sex difference in the metabolism of galactose, but one record of a similar study was recorded in the literature. Artom (44) found that spayed bitches possessed an unchanged tolerance for invert sugar.\* More recently, Tsubura (34) using glucose, has observed that castration of rabbits of both sexes lowered sugar tolerance. Estes and Burge (47), using *paramecia*, have demonstrated an increased sugar consumption by the organism under the stimulus of ovarian hormone. Burge and Williams (48) had previously noted a similar effect with insulin. In presenting the data here assembled, a word of explanation is necessary. As the entire matter has been discussed at length elsewhere (49), only brief explanatory notice is offered here. While the galactose tolerance of the male is totally uninfluenced by age or level of reproductive activity, the female tolerance is seemingly directly dependent upon the maturity and condition of the ovaries. Briefly, the prepubertal child gives a positive test with 20 grams; with the onset of the catamenia she advances to 30, and ultimately (usually within the year) to 40 grams, the normal level of the adult matured woman. With the menopause the tolerance level may remain at 40 or sink to 30 grams.† With a changing tolerance, the individual records of the tolerance dose in grams are insusceptible to collective reporting. By expressing changes in tolerance as percentage variations from the norm of the given individual, data are produced which possess a parity in their indications. Although the male tolerance is a constant, the same method of expression is adopted for the sake of uniformity. The data are given in Table VIII.

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\*De Fellippi (45), quoting Quarta, recorded a result similar to the writer's with dogs, using glucose as the test sugar. Allen (46) denied the validity of these findings.

†It is not to be understood that abrupt transitions take place. The figures given are conditioned by the method of applying the test, which has been fully described elsewhere (50).

TABLE VIII  
GALACTOSE TOLERANCE (1)

Observation	Unit	Male	Female
Tolerance Dose.....High	Grams	30	30
Low	Grams	30	20
% above normal.....	%	0	0
% equal normal.....	%	100	0
% below normal.....	%	0	100
Average Deviation from normal.....	%	±0	—44

1. The following cases are omitted from the tabulation as superimposed non-endocrine disturbances mask the gonad influence:

- Two male castrates with tolerance at 40 gms. (+33%) had demonstrated late chronic interstitial nephritis.
- Three aged females showing normal post-menopausal tolerance (30 gms.) had demonstrated severe chronic interstitial nephritis.
- Four females, with tolerance averaging —80% below normal, were suffering severally from lesion of central nervous system (2), syphilis (1), and liver disorder (1). These conditions exercise a definite depressing influence on sugar tolerance.

The differences here exhibited are of the utmost diagnostic importance. Castration in the male is without influence on the galactose tolerance. Seemingly the testicle is not concerned with the regulation of the galactose metabolism. The effect on other sugars is at present unknown and is to be investigated. The omission of two male cases not recorded in the table is explained in the foot note.

Incidentally, the lessened permeability of the kidney, arising in an established nephritis, is a factor that should be considered in all forms of tolerance testing depending on urine findings. Unimpaired permeability should be demonstrated by test, and if there be indication of lowered kidney function, due allowance must be made in the interpretation of results.

Reverting to the table, we find that in every case lowered activity of the ovaries determine a lowered galactose tolerance. Further, in the castrates and severe functional failures, the level is at 20 grams. With the incipient or less severe functional cases the depression is less i. e. to 30 grams. It must be remembered that this series includes only females in whom the menstrual function has been established. What the effect would be of castration in prepubertal years is now a matter of conjecture, but from the data here and a number of unpublished observations, it seems probable that the prepubertal level of twenty grams would remain unaffected.

The striking point, from the standpoint of differential diagnosis, lies in fact, that while failure of the posterior lobe of the pituitary raises tolerance to a marked degree, and thyroid failure exercises either no influence or produces a slight increase, loss of function of the ovaries determines a decrease in tolerance to apparently a low limit of 20 grams. [The four cases which we have studied showing lower tolerances are already covered by the foot note (3) of the table.] The failure of the testicle to affect the galactose metabolism has only a less diagnostic significance, and indirectly bears upon other germane problems to be discussed later in this paper.

Before taking up the next portion of this paper, a word of explanation is necessary.

It will be noted in the foregoing discussion that but meager reference is made to the work of others. There is, of course, a most extensive literature bearing upon the subject in general, and ranging from the admirably careful, painstaking studies involving a wealth of experimental data, to those treatises designed to exploit some method of rejuvenation based upon manipulation of the organs of generation. Unfortunately for comparative purposes, a vast amount of this work deals with animal experiments that are inapplicable to the thesis in hand. A further hampering condition lies in the concentration on changing secondary sex characteristics as criteria of modified internal secretory activities. As these are certainly influenced by other agencies, at least in man (see discussion above), such observations, while striking and of the utmost import, bear but little relation to the work in hand. For example, so admirable a compilation as that of Lipschütz (4), collating a vast amount of original research with an equally exhaustive and selective canvass of the literature, contains no reference to the influence of the gonads on many important phases of metabolism. Again the emphasis laid upon the reproductive powers, which are certainly not solely intrinsic in internal secretory activity, obscures the issue.

Such pertinent observations as we have found in the literature have been incorporated in the running comment on the data reported by us. The meager tale of citations attests solely to the relatively slight consideration that has been given to this field of study.

PART II

Turning next to the clinical aspects of the condition, in reviewing the literature one is impressed with the lack of clear-cut definition of the hypogonad syndrome. It is true that a vast bibliography exists dealing with the influence on menstruation and on fertility. But there is missing, so far as the authors can ascertain, those graphic pictures so frequently presented in descriptions of many of the other endocrinopathies. There are, however, a few definite symptoms upon which observers are agreed, and these together with the more frequently considered features of the reproductive function will be considered in the light of our own findings. For obvious reasons, the two sexes will be discussed separately. The ovarian group has been augmented by a few later cases, and unless otherwise specified, the later statistics will derive from this larger series. The composition is given in the next table. Interesting members of the several groups will be discussed in detail later.

TABLE IX  
OVARIAN GROUP

Primary Ovarian Failure.....	200
Castrates (premenopausal) (1).....	21
Castrates (postmenopausal).....	2
X-Ray Sterilization.....	1
Female Pseudo-Hermaphrodites.....	2
Practical Amenorrhocias (2).....	2
TOTAL.....	228

(1) Operated upon at an average age of 38 years.

(2) One of these, matured at 17, nearly 3 years later had had but 3 periods; the other matured at 14 and had had 4 periods in 11 years.

Practically all of the patients in the group were American born. No racial incidence was traceable in the very imperfect records available. The family history can best be presented in tabular form. The records are confined to immediate relatives. A number of the patients reported "nervousness" as a common familial trait. The term is an elastic one, and as applied to an immediate family may only reflect the patient's own nervous

TABLE X  
FAMILY HISTORY

<i>Disease</i>	<i>Per Cent</i>
Cancer .....	20
{ Diabetes .....	8 }
{ Other Endocrine.....	5 }
Tuberculosis .....	23
Insanity .....	11

instability. The mental attitude of the patient with ovarian failure is touched on below.

A review of the chief complaints as offered by the patients themselves is most informative. In some cases, more than one disability was recorded as of basic importance, which explains the numerical discrepancy. Small groups without primary significance have been omitted.

TABLE XI  
CHIEF COMPLAINTS (PATIENTS')

Fatigue .....	72
Headache (1).....	35
Mental and Nervous Disorders (2).....	55
Convulsions.....	7
Gastro-Intestinal Disorders.....	20
Pain (1).....	23
Menstrual Disorders (3).....	28
Sterility (4).....	6
Obesity .....	21
Vertigo .....	8
Deafness .....	20

(1) Not primarily associated with menstruation.

(2) Fourteen Psychoses with 5 attempted suicides, 11 Psychoneuroses, 30 Neuroses.

(3) See Table XV.

(4) See Table XVI.

Fatigue and weakness, cardinal symptoms in the other endocrinopathies, here characterize one-third of the entire group and as a secondary feature, they appear in the majority of the remaining cases. Headache is another important part of the clinical picture. Its dominance has already been noted in the pituitary and thyroid groups also. The number of established



psychoses is interesting. A causal relationship here is still to be demonstrated; the observation, however, is possibly suggestive in the light of known mental deviations associated with physiological modifications of ovarian activity. Irritability and depression are frequently mentioned as features of a failing ovarian function. Record as to the first must depend almost exclusively on outside information, as the egocentric "hypogonad" usually lacks a philosophic objectivity in personal prospective. The authors have previously noted, however, the definite warrant for the inclusion of this sign as a most characteristic finding. Many of the patients name the second as a feature of their general condition.

In this connection a few words may not be inopposite on personality changes associated with depressed ovarian function. Comment has already been made of a similar condition in thyroid disease although the formula of its expression differs from that produced by ovarian failure.

An insistantly expressed egoism is the keynote of the hypogonad character. Coupled with, and dependent on, this is an active resentment toward a world that is but inadequately mindful of the patient's many excellencies. Hyper-emotionalism and self-pity are united with an attitude of acid criticism of environmental conditions that are always unsatisfactory. The psychological study of the average woman suffering from ovarian insufficiency would be a profitable though scarcely a pleasant task.

The cases presenting convulsions were practically all established cases of epilepsy. Again, a causal relationship remains to be established. Gastro-intestinal disorders are among the well recognized sequelae of ovarian failure. In this group, four patients had demonstrated gall bladder disease, and but very few failed in their histories to give some evidence of disorder of the alimentary tract. Constipation was an usual finding, 54 per cent recording it as a chronic state. Only five patients complained of diarrhoea.

Pain, as such, was offered by 10 per cent of the patients as a primary cause of disability. Localization was rarely specific, although the lower half of the trunk was usually included in the picture. In a few cases, at least, a very definite subjective element was demonstrable.

The cases presenting menstrual disorders and sterility will be touched upon later. Twenty-one patients offered obesity as a principal difficulty. As a matter of fact, 71 of the group were over 15 per cent above prediction and in many instances, far in excess of this modest level. On the other hand, an equal number were more than 10 per cent below their calculated weights (Dreyer) while the remaining 38 per cent fell within these reasonable limits. From these figures it is clear that ovarian failure certainly does not always determine obesity. Tandler and Grosz (14) have described a "tall" type but the emaciated group does not conform to this designation. In this connection, it seems to the writers possibly significant that with the pituitary there is the non-obese Lorain-Levi type of failure; they have themselves described an underweight hypothyroid type; while in the ovarian group, as many are significantly under as are overweight. The underlying metabolic disturbances deriving from endocrine malfunction would seem to manifest themselves uniformly in a variety of ways.

In 8 of the cases, vertigo was a primary complaint, while a large number of the remainder gave it as one incident in the general disease picture. Hot flashes were by no means so common as might be inferred from the usual records in the literature. The majority, but not all, of the postmenopausal patients, both of natural and surgical origin, reported this symptoms, but it was conspicuously absent from the histories of a large part of the younger women. This would suggest, perhaps, that it is significant only in the more severe established cases and a sign of a marked hypofunctional level.

The age of onset and the duration of the chief complaint is potentially interesting. With many of the presenting symptoms, the onset was undoubtedly gradual and their first recognition coincident with some event which was, in many instances at least, unrelated to the underlying disorder.

The relatively large percentage reporting an onset during the years of adolescence and early childbearing is a possible point of interest though too great weight should not be placed upon it in view of the uncertain character of the data from which it derives. A second feature in the table is the upward progress of the duration until the menopausal age, at which

TABLE XII  
ONSET AND DURATION OF CHIEF COMPLAINT  
(200 Consecutive Cases)

<i>Interval</i>	<i>Age of Onset</i>	<i>Average Duration</i>
From birth	6.0%	26 years
0-10 years	3.3%	
11-20 years	32.0%	3 years
21-30 years	31.3%	6 years
31-40 years	16.0%	9 years
41-50 years	6.7%	13 years
51-60 years	2.7%	11 years
61-70 years	2.0%	12 years

time it apparently becomes stationary. This too may be an artefactual relationship; it is recorded only as a statistic.

The incidence of the more common infections as derived from the history has been reduced to tabular form. The relative frequencies would seem to indicate a definite degree of susceptibility to the commoner complaints.

TABLE XIII  
INCIDENCE OF EARLIER INFECTION

<i>Disease</i>	<i>Per Cent</i>
Measles .....	86
Whooping Cough .....	61
Mumps .....	50
Chicken-pox .....	49
Influenza .....	30
Scarlet Fever .....	22
Pneumonia .....	12
Diphtheria .....	11
Rheumatic Fever .....	10
Typhoid .....	9

Yet another datum is found in the record of previous surgical manipulation of the pelvic organs. As already noted (Table IX), there were 23 castrates in the series of 228 consecutive cases. In addition to these were the following: (See Table XIV.)

In other words, including the castrates, one woman in every four had had at least one laparotomy (several reported as many as four or five) for surgical manipulation of the pelvic organs,

and 7 per cent more had been curetted for reasons unassociated with any of the incidents of pregnancy. Several of such matters will be discussed at length in a later paper.

TABLE XIV

Laparotomy for	
Unilateral oöphorectomy .....	14
Resection of ovarian cysts.....	5
Resection of uterine fibroids.....	2
Uterine abscess .....	2
Uterine suspension .....	12
Therapeutic curettage	
(excluding miscarriage) .....	16

The importance of a thorough physical examination has been stressed throughout these papers. A few of the more significant observations may next be recorded.

The prevalence of skin eruptions is one usual finding that our records do not entirely confirm. Acne was common, it is true, but this mild inflammatory condition is associated with too many other disease states for it to assume any specific meaning here. But three of the entire group recorded skin eruptions as major complaints, two with eczema and one with psoriasis. Vulval pruritis is usually considered to be a frequent manifestation and this is scarcely to be wondered at, in the light of the frequent incidence of glycosuria. Two of our cases presented this condition as a complaint and a number of others recorded earlier attacks.

In view of the frequent allocation of hypertrichosis to adrenal disease, our own figures are of more than passing interest. Unfortunately, no record of pilosity was made in some of the earlier cases. In 134, however, in which complete observations are reported, 62 or 46 per cent showed marked hypertrichosis and of these, 45 had a definite male configuration of the pubic hair. As already noted, Falta's cited cases of adrenal disease with virilism all showed a concomitant ovarian involvement whenever record was made. The authors do not feel that their own observations settle the question; they record only a number of cases presenting excessive pilosity with retrogression of certain secondary sex characteristics, in which no evidence of an adrenal complicity was demonstrable. True, the pluriglandular

enthusiast might adduce this observation to support his thesis. but the hypernephromata associated with virilism are commonly interpreted to indicate adrenal overfunction, a condition that would ill accord with many of the laboratory findings in this series. Further, if pubertas praecox derive in many cases from adrenal overfunction, one faces again an antithetical and contradictory series of facts which cannot be explained away.

Nearly 10 per cent of the cases presented deafness as a chief complaint. As one of the author's associates has shown [Drury (51)] endocrine failure may be a factor in otosclerosis, and a number of these patients were referred for study on that basis. A fraction of them proved to be true otosclerotics, but the remainder demonstrated defects of infectious origin, establishing a purely non-endocrine etiology for the deafness.

That the calcium metabolism is influenced by the level of ovarian function is generally conceded although the mechanism must be regarded as wholly unknown.

One-third of the entire series showed evidence of past or present gravely defective teeth, while an additional 12 per cent were reported with the teeth in "fair condition" only. The cross section of the social background of the group precludes neglect as the primary causal agent.

Diseased tonsils have already been noted as of very frequent occurrence in pituitary and thyroid disease. The present group offers no exception to the previous record. Forty-four per cent of these patients had had one or more tonsillectomies, while the laryngological examination showed an additional 24 per cent with definite tonsillar infection. The total of 68 per cent compares favorably with the incidence of all of the commoner infections with the exception of measles. Whether a disturbed metabolism of endocrine origin predisposes to a lowered resistance to infection or focal infections influence selectively the level of endocrine function, is a question for the future to settle. The high coincidence in the conditions discussed would seem to indicate a possible inter-relationship.

A number of the patients (15 per cent) showed some thyroid enlargement, in fact several of these were referred as probable thyroid cases. In no case was the enlargement marked and equally, in none of them was thyroid disease demonstrable.

Residence in so-called goiter districts, the sequelae of child bearing and similar agencies, were apparently responsible for the occurrence of these non-toxic goiters.

The routine heart examination developed reportable abnormality in 20 per cent but grave cardiac conditions were rare. As previously noted, 10 per cent of the group had had rheumatic fever. Similarly, while 16 per cent gave evidence of past or present pulmonary disease, a number of patients with a history of asthma or hay-fever and a few cases of healed tuberculosis accounted for practically all of them. In no case was there any apparent relationship between any chest condition and the presenting endocrine disease.

A general tenderness on deep palpation of the abdomen was reported by 11 per cent of the group. In view of the surgical histories recorded, added to the subjective attitude of many of the patients, the number is small. The gall bladder cases all showed tenderness in that area, but with the others, the definition was usually vague.

Diminished or exaggerated reflexes were exhibited by one in three, but beyond these and one doubtful Babinski, the routine neurological examinations were not remarkable.

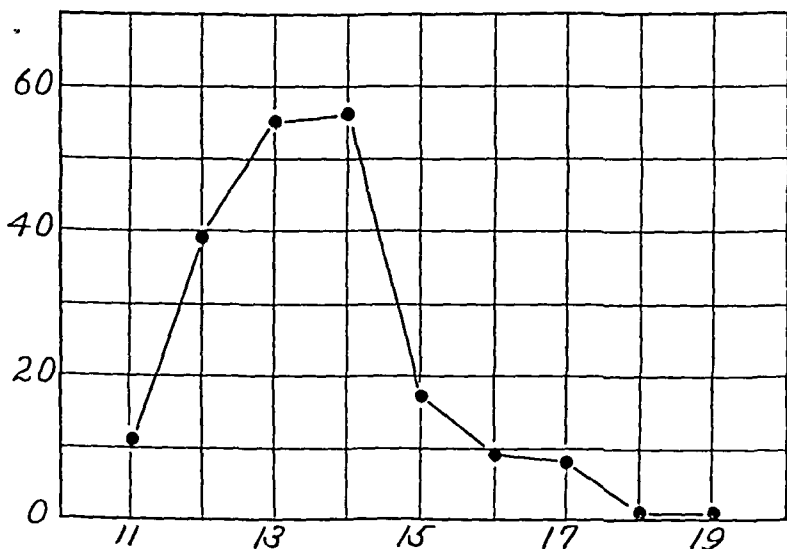
Turning now to a consideration of the exocrine functions (in the regulation of which, in the last analysis, endocrine activities may be implicit), the age of the establishment of the catamenia invites attention. The accompanying graph (Graph I) gives the records of 197 cases in this series. One child maturing at 7 and the two pseudo-hermaphrodites are not included. Seventy-five percent fall within the conventional 12 to 14 year limits, while over half (28) of the remainder impinge upon the chronological limits of the restricted group. Ten per cent only, show a definitely retarded maturity; two of the patients are in the group later castrated, a rigorously just proportion. If the figures obtained are meaningful, ovarian failure would seem to be either an incident of the years of maturity or, if a prepubertal existence be assumed, without signal influence on the fact of maturation. One child had a unilateral oöphorectomy at 12 and menstruated at 13. The others were operated upon much later and after maturing. The subsequent menstrual histories are presented in tabular form.

TABLE XV  
MENSTRUATION (214 CASES)

Period	—Amount of Flow—		
	Diminished	Normal	Increased
Irregular (39%)			
Increased .....	14	36	13
Decreased .....	3	5	9
Both .....	1	0	3
Total .....	18	41	25
Regular (61%) .....	23	83	24
Total .....	41	124	49
	19%	58%	23%

Regularity and amount of flow are the two variable elements considered. In view of the frequent statement that ovarian failure presupposes a disturbed menstrual function, these figures are enlightening. Nearly two-thirds of the group record a normal rhythmic incidence of the function, and a slightly smaller number present a normal flow. Eighty-three (39 per cent) are both regular in rhythm and normal in amount. Another usual statement that ovarian failure shortens the interval is far from substantiated by these records. Of the irregular

PLATE I



Maturity curve. Number maturing at each year. Omits one child menstruating at seven years, and two female pseudohermaphrodites who never menstruated.

group, only 17 show an accelerated recurrence, while nearly four times that number have delayed periods. If one considers the absolute incidence of shortened interspace in the entire series, the percentage shrinks to wholly unconvincing proportions. Four patients, only, show that double irregularity which is so common a feature of thyroid failure. Avoiding dogmatism, it may be said that in this series, ovarian failure has a tendency to lengthen the menstrual interspace in that smaller proportion which depart from the conventional rythm.

One very striking fact may be commented on in passing. In Table X, only 28 of the patients offered menstrual disorder as a chief complaint, although 84 report irregularity of the function and 24 an increased flow. Even more significant is the fact that 136 of the group reported dysmenorrhoea of varying degrees of severity. The disproportion between the actual incidence and its presentation as a disability emphasizes the pathetic acceptance of painful menstruation by the average woman as a normal complement of the exercise of this particular physiological function.

It will be remembered that six of the patients offered sterility as the cause of presentation for study. The fertility data are interesting in this connection. It should be stated that, of the augmented group, 121 were unmarried (53 per cent) and the remainder had had one or more matrimonial experiences. The relative equality of the two groups may bear on the elimination of sexual inactivity as a predisposing cause to gonad failure. In the writer's opinion, the series is too restricted to indicate more than a possible trend. The fertility data are given in Table XVI.

TABLE XVI  
FECUNDITY (100 CASES)

Group.....	I	II	III	IV
Miscarriages.....	0	A = 2	0	Av. = 2(1)
Children.....	0	0	Av. = 2	Av. = 3
Number.....	31	10	34	25
Duration of Marriage—				
Longest.....	32 years	21 years	30 years	28 years
Shortest.....	1 year	2 years	3 years	2 years
Number < 5 years.....	13	4	2	1
Total Average.....	8 + years	11 + years	13 + years	18 years

(1) Omitting 1 case with 24 miscarriages. See text.



Four permutations are possible as exemplified in the four groups. In all the cases recorded, contraception was specifically denied. When this has been practised the degree of fecundity in the non-pregnant naturally remains a matter of conjecture. For obvious reasons induced abortions are likewise omitted.

Nearly one-third have never been pregnant, while 10 per cent more have conceived but have been unable to complete their pregnancies. While lues cannot be ruled out absolutely in any case, all of the patients presented here, with but two exceptions, had negative Wassermans and, in many cases, negative Kahn tests as well. The two exceptions fall in Group IV, having borne children as well as having had miscarriages.

Forty-one per cent of these patients were sterile at the time of study and, even if these subjects be deducted who had been married less than five years, the remainder (24 per cent) falls notably above the average percentage of infertility as recorded by others. Reynolds and Macomber (52) conclude that from 10 to 12 per cent represents a fair measure of infertility and in this estimate they are unable to eliminate those arising from contraception. On this basis the present figures show an augmented degree of infertility of striking proportions. One-third of the group have completed all of their pregnancies successfully and one-fourth have conceived several times with average result of 60 per cent productivity. As noted above, one case is omitted from the computation of the miscarriages since, after bearing one child, she subsequently had 24 incomplete pregnancies, the husband being luetic. The point of note in this case is the very high initial fertility of the couple which, in spite of all handicaps, permitted 25 impregnations. The patient's weary tale was ended by a panhysterectomy several years before entering the clinic. At no time did she give any evidence of specific disease and at the time of her study the serological tests were uniformly negative.

As was stated in the first paper of this series and reiterated in the later discussions, the various special examinations serve the primary purpose of determining the presence or absence of a non-endocrine disorder to which the patients disabilities may be referred. Only exceptionally, and this is peculiarly true of the present group, do they add positive evidence of an endocrine

involvement. A brief partial analysis of 100 selected cases in which a total of 574 special examinations\* were performed, may be considered.

*Eye:* Of a total of 90 examinations, 72 gave positive findings. Enlarged blind spots were found in 46, while patients with disc defects such as tallow color, indistinct margins, etc., were 24 in number. Twenty-two showed contracted fields, of which 6 demonstrated a symmetrical contraction of marked degree. Stiff pupils were found in four cases, and two showed the so-called "snuff fundi" usually regarded as a sign of congenital syphilis. Two scotomata were delineated and one case a recognized atrophy of unknown cause.

*Ear:* Of 20 ear examinations, 7 showed infective processes and the remainder defined otosclerosis. One-third of 18 Barany tests gave positive evidence of labyrinthine disease. Fourteen of 22 audiograms showed marked loss of aural acuity and the remainder indicated only a lesser degree of impairment.

*Neuro-psychiatric:* Examinations were made of 63 of the series. The results can be presented in tabular form.

TABLE XVII  
NEURO-PSYCHIATRIC DIAGNOSES

Psychoses .....	9
Psychoneuroses .....	6
Neurasthenia .....	11
Hysteria .....	2
Epilepsy .....	6
Organic disease .....	7
Chorea .....	2

The seeming discrepancy between these figures and certain of those recorded in Table XI is due to the fact that a number of the patients were referred from institutions where the nervous and mental elements had already been evaluated.

*Radiography:* Ten patients showed small, shallow or otherwise remarkable sellae. None of them gave evidence of pituitary tumor. The impossibility of delimiting the normality of the sella

\*The average for the entire series is slightly less than three per person. In many instances "Short Form" subjects fail, for a variety of reasons, to return for all of the special tests requested. Averages in later series, however, are much higher, i. e., "Long Form" 8+, "Short Form" 5+.

shape has already been noted (53). Sinus involvement was found in 14 of the cases studied. A past or present pulmonary disease was demonstrated in 13 patients; six of these showed a protein sensitivity. Seven gave x-ray evidence of cardiac enlargement, confirming the number demonstrated by the electrocardiograph. Eight out of 13 gastro-intestinal series showed disease, chiefly in the appendix, while one Graham test (intravenous) was positive in five performed.

*Pelvic:* Of the 55 cases examined, 13 gave evidence of some disorder, chiefly in the uterus. One infantile and one juvenile organ were found; the others were chiefly fibroid tumors.

Of the numerous other examinations, none gave data of sufficient interest to warrant comment. It will be noted from the above that none of the findings were especially pertinent to the positive determination of endocrine disease. Even the eye results, although they indicate a large degree of metabolic disturbance, fall short on any specific endocrine indication, in this group.

Limited as are the clinical indications, outside of the functions intrinsic in reproduction, which are regarded as characteristic of ovarian failure, the complementary testicular picture is even more circumscribed in detail. The study in adult years of males castrated in childhood offers some help, it is true, in defining characteristics of what may be designated as early eunuchoids. But without more objective methods of analysis than have been applied to this problem, there is always the unresolved question with the latter group if the observed genital arrest is more than one secondary evidence of early pituitary or thyroid disease—resultant and not causal. Studies of adult castrates whose glandular ablation has occurred after maturity has been established are extremely rare in the literature. Falta (21) comments on this and, in spite of the wealth of clinical material at his command, is constrained to present as his illustrative case an individual who contracted gonorrhoea with bilateral orchitis and, later, lues before tuberculosis necessitated a bilateral orchidectomy which lessened but did not obliterate his libido et potentia coeundi at the age of 26. In his 37th year he had a goiter which later spontaneously receded, and Falta saw him seemingly when 49 years of age. Falta comments on the disturbing elements, but states that the patient recorded his

modified habitus as first appearing after the operation.

The overgrowth of the long bones due to retarded epiphyseal closure, the lowered sitting height index arising from this cause, and a gradual assumption of an outward female habitus with modified pelvic contour are primarily referable to failure in youth. Even so, Tandler and Grosz (14) recognized both a fat and a tall type, although they state that the latter manifest a tendency toward characteristic fat desposition.

The four eunuchoid cases in this group show respectively sitting height indices of 0.514, 0.520, 0.525 and 0.550—in other words, one only, the 10-year-old child exhibits a significantly low value, while another is markedly above the normal average.

A loss of body hair with a feminization of the pubic contour is not confined to malfunction of the testicles, as numerous pituitary studies have shown. A wrinkled skin and some pigmentation are other features recorded, but in the main, there is a notable dearth of informative and suggestive detail. That this should be the case is in no small measure implicit in our findings. As has been emphasized repeatedly in these papers, male castration in adult years produces but minor changes in functional levels as ascertained by objective methods. In the main, the physical picture of the adult castrate presents a definite and general normality. The present small group is composed of men castrated in adult years (3), of cases of bilateral orchitis as a sequel to mumps in the years following puberty (4), and boys and young men exhibiting a marked arrest of sex development (4) in whom no evidence of pituitary or thyroid disease could be demonstrated by careful and detailed study.

With so small a group and one so divergent in the several elements that compose it, a statistical analysis is meaningless. A few comparisons may be drawn with certain of the more significant findings in the ovarian group. Five of the eleven gave fatigability as their chief complaint, and the majority of the remainder reported it as an important secondary symptom. Four were referred for genital underdevelopment, and two for sterility. Of the eight adults but three were married, and all were sterile save the aged man whose orchidectomies had been performed in the preceeding two years. One of the castrates subsequently married and was able to have intercourse with his wife

to her satisfaction (see case B-42 in next section). Diseased tonsils were again prominent, five having had them removed, while four others showed infection. Three of the four eunuchoids (10, 13 and 16 years) were of an obese feminine physical habitus, the remaining patient being spare but with somewhat broad pelvis. Body hair was usually scanty although this feature, as one might anticipate, was less marked in the castrates and post-orchitides. Constipation was an almost uniform finding, even more markedly than in the female group. The other findings lack a sufficient degree of concordance to be significant.

In the next section, typical case protocols from each of these groups will be given and will serve to elaborate the thesis presented above.

### PART III

#### CASE PROTOCOLS

To complete the paper, the authors desire to present a few of the cases in detail. In reviewing them, the reader is reminded that many of the factors contributing to the diagnosis could not be included here. Emphasis will be laid upon those points which may be correlated with the matters which have been discussed in the earlier pages.

#### GROUP I. GENITAL ANOMALIES.

**CASE B-21. PSEUDOHERMAPHRODITE.** The patient's chief complaint was of obesity from which she stated she had suffered since early childhood. The history which we obtained was very limited and as events transpired not entirely ingenuous. During the course of the study several anomalies in the laboratory picture developed, and as a result one of us questioned the patient much more searchingly in regard to her history. She then acknowledged that she had never menstruated and was what was called an "hermaphrodite." She had been cognizant of this condition since early childhood but her family, for religious reasons, had refused to allow any physical examination and in the few years that had elapsed since their death the earlier inhibition had persisted.

*Family History:* Was entirely devoid of significant information.

*Past History:* The patient reported minor ailments and, later, the information given above.

*Physical Examination:* The patient was markedly obese, the hair soft and abundant, the thyroid not enlarged; the breasts were mod-

erate in size and essentially feminine in contour. There was reported a slight cardiac murmur at the apex which was later denied. There was abundant pubic hair with a tendency to male configuration, marked pilosity on the legs and a slight mustache. Routine neurological findings were normal.

*Laboratory Summary:* The patient was 33 per cent overweight; a basal rate of —11 per cent was recorded, and this was probably somewhat above the truth; blood pressure was low. Alveolar CO<sub>2</sub> was a low normal. The residual nitrogen fraction of the urine showed an upward tendency. Galactose tolerance was half the normal for a woman of the patient's age. The urea curve was normal. The blood morphology showed a substantially normal picture.

*Radiographic findings* of the skull and sella were normal.

*Pelvic examination* disclosed a congenital absence of the vagina and a prominent clitoris 1½ cm. in diameter.

*Discussion:* The general picture presented was that of ovarian failure. Because of the patient's obesity and the other impediments it was impossible to demonstrate the ovaries. One interesting fact

TABLE XVIII

	Genital Anomalies				Homosexual	
	1	2	3		4	5
Case Number.....	B-21	B-946	B-812	B-1008	B-408	B-530
Sex.....	F	F	M	M	F	F
Age.....(yrs.)	34	4.5	4.5	5.0	36	19
Height.....(cm.)	166	120.5	129.5	137.4	164	169
Weight.....(kgm.)	83.5	23.2	28.3	33.2	43.6	79.2
Weight Deviation.....(%)	+33	-19	-19	-22	-29	+23
Lung Volume Deviation.....(%)	—	-2	-43	+3	-27	-4
Basal Rate Deviation.....(%)	-11	875 cal.?	1058 cal.?	1260 cal.?	-13	+5
Blood Pressure.....(mm.)	110/78	96/50	96/53	104/56	102/62	110/62
Pulse Rate.....(per min.)	66	88	70	86	76	71
Temperature.....(deg. F.)	98.0	98.0	98.2	98.8	97.9	99.0
Alveolar CO <sub>2</sub> .....(mm.)	39	43	42	38	31	38
Urine Volume.....(cc.)	1440	380	530	1120	440	1420
Spec. Grav.....	1.015	1.028	1.024	1.015	1.029	1.020
Albumin.....	0	+	0	+	0	0
Casts.....	0	0	0	+	0	0
Sugar.....	0	0	0	0	0	0
Total Nitrogen.....(gms.)	10.73	5.37	6.35	8.11	5.42	11.74
Residual Nitrogen.....(%)	8.4	10.9	16.0	10.7	5.8	5.4
Phen. Sulph. Phthal.....(%)	72	63	65	60	64	49
Galac. Tol.—						
Normal.....(gms.)	40	20	30	30	40	40
Observed.....(gms.)	20	20	10	20	20	20
Deviation.....(%)	-50	+0	-67	-33	-50	-50
Blood—						
Non-Protein Nitrogen.....(mgm.)	27	32	32	30	32	32
Uric Acid.....(mgm.)	3.5	3.8	3.2	3.5	2.2	3.3
Sugar.....	98	100	75	83	87	86
Haemoglobin.....(%)	100	85	98	95	90	90
Erythrocytes.....(10 <sup>6</sup> )	5.76	4.11	6.63	5.32	4.39	4.51
Leucocytes.....(10 <sup>3</sup> )	10.40	8.55	8.50	12.45	8.00	5.70
Neutrophils.....(%)	68	47	55	56	32	55
Lymphocytes.....(%)	29	44	31	30	63	38
Eosinophiles.....(%)	2	3	0	2	1	2
Monocytes.....(%)	1	0	14	12	4	5
Misc.....(%)	0	0	0	0	0	0

1. Pseudo-hermaphrodite (female).
2. Pseudo-hermaphrodite and Pubertas Præcox (female).
3. Pubertas Præcox (male).
4. Homosexual (male).
5. Homosexual (female).

\*Observed heat production (see below).

given by the patient was that for many years she had had a headache which would last about one day, and which came at four-week intervals. During the day of the headache she had frequently noted that her perspiration had a peculiar and somewhat offensive odor. From the fact that the secondary sex characteristics had developed, it seems fair to assume that the patient presented a genital inadequacy, and that some ovarian tissue was present. Another point worthy of note was that her sitting height index was practically normal, the long legs of the so-called eunuchoid being absent. A surgical opinion was requested and it was decided that there would be no real advantage to the patient through surgical interference.

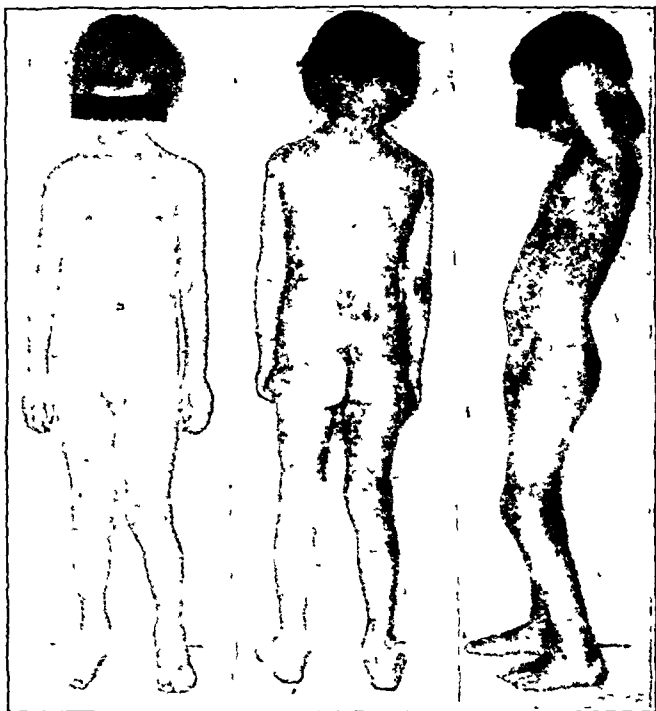
**CASE B-946. PSEUDOHERMAPHRODITE WITH PUBERTAS PRAECOX.** This little patient was a child four years and seven months of age who was first seen in the Out-Patient Department. The family physician had referred her for an investigation of a definite genital anomaly. The child had a hypertrophied clitoris resembling the penis of a boy of 12. In addition there was a definite growth of pubic hair although the breasts were still rudimentary. Outside of the genital condition the child was in perfect health. The study was undertaken to resolve the sex of the patient and equally to ascertain the cause of the precocious puberty.

*Family History:* The father, mother, and one older sister are living and well and present no anomalies. A second child, a male, born before the patient, cut his first tooth at eleven months, talked at twelve months, walked at sixteen months, and weighed 40 lbs. at the time of his death from meningitis shortly before his second birthday. The patient's genital anomaly was recognized when she was but a few days old. The family physician, however, most judiciously advised delay in attempting any modification.

*Past History:* The patient weighed 10 lbs. at birth, cut her first tooth at eight months, talked at twelve months, and walked at eighteen months. She had pertussis at 2½, discharging ears for about a fortnight at eighteen months, but had otherwise been a strong, active, healthy child.

*Physical Examination:* The patient was a well developed, somewhat undernourished child between four and five with abundant hair on the head; a suggestion of slight exophthalmos was noted, but other observation demonstrated that this was a familial characteristic. Her ten upper and ten lower teeth were in fair condition. The tonsils were large and cryptic. The voice was somewhat deep and the speech slightly thick. A single pea-sized gland was felt in the upper right anterior cervical chain. It was not tender. The breasts were undeveloped and the nipples suggested the male type. The heart, lungs, and abdomen were normal. There was a considerable amount of brown pubic hair extended from the upper border of the symphysis, separating on either side of the hypertrophied clitoris. This latter was 4 cm. long, 1.3 cm. in diameter, and suggested a penis and glans after circumcision. There was no evidence of any orifice. The whole structure curved downward over an opening immediately beneath it about 1 cm. in diameter. At the upper edge of the apparent vaginal orifice could be seen the urethral opening. The vaginal slit was overhung by folds of hair-covered skin resembling labia majora. There was no evidence of scrotum, testicles, or patent inguinal canals. During the examination the clitoris became erectile. There was no axillary hair or other abnormal pilosity. The patient's gait on walking was noted to be a little clumsy.

## PLATE II



Case B-946

## PLATE III



Case B-946



*Laboratory Summary:* The child was distinctly tall for her age, 19 per cent under her predicted weight, and with normal lung volume. The basal rate was determined by a series of observations as 875 calories. Comparison with the age standard, which would be obviously unfair, gave her a value of +17 per cent. With the area, height and weight standards of Benedict-Talbot (54), the observed and predicted practically coincided. By the Harris-Benedict (24) standards and the Bailey (55) area computation, she was about 20 per cent below prediction. It may be safely said that the child did not present a high basal rate and it was our feeling that the rate was probably slightly though scarcely significantly low. The blood pressure was low, the pulse slightly rapid.  $\text{CO}_2$  was normal. The several urines showed a very scanty volume with good elimination in relation to the patient's weight. Albumin was constantly observed. The average protein intake was somewhat low, the residual nitrogen fraction high. She reacted positively with 20 grams of galactose, negatively with 10. This would be normal value for a female child in the prepubertal period and a depressed tolerance for a boy of the same age. The blood uric acid was relatively high. The blood was lymphoid in type, showed a 3 per cent eosinophilia, and a slight secondary anaemia.

*Audiogram:* Showed substantially normal hearing.

*Ear Examination:* The ear drums were markedly thickened.

*Barany:* Normal reactions were obtained.

*Nose and Throat Examination:* The tonsils were enlarged but not demonstrably offending.

*Chest Examination:* The findings were normal.

*Neurological Examination:* The examiner regarded the patient's gait as normal and found no evidence of organic nerve lesion.

*Pelvic Examination* confirmed the statement given above, and noted that the labia were rather rudimentary and defined the existence of a vagina. No internal genitalia could be palpated, which would be explained by the patient's youth.

*Radiography:* The skull showed a persistence of the frontal suture and convolution impressions on the inner table. The sella and sinuses were normal. The chest was normal.

*Cardiogram:* Normal findings were obtained.

*Eye Examination:* The patient was too young to permit delineation of the visual fields. The fundi showed snuff pigmentation throughout.

*Urea Index:* A normal value of 155 was obtained.

*Lumbar Puncture:* This was felt necessary in view of the eye report. The pressure was 18 cm., rose to 26 cm. on pressure, returned to 18 cm. with removal of pressure. When 15 cc. of fluid was removed the pressure fell to 12 cm.

*Spinal Fluid* was strictly normal.

*Discussion:* At this point there were two definite problems to be considered. First, the sex of the child, in order that the interpretation of the various laboratory data might be as exact as possible. There was, further, the important social problem which could become acute in the course of a few years. The second question was the basis of the patient's precocity. Three endocrine factors come certainly

into question, with possibly a fourth. Over-activity of the gonad, pituitary overproduction, and tumor of the adrenal cortex have all been recorded as causative agents. While the case for the first is less well sustained and would probably imply tumor growth, it can not be ignored. The fourth possibility is, of course, the pineal, but here the evidence is even more doubtful. If the child had a cortical tumor, surgical intervention was essential, and as they are usually malignant the time factor had to be reckoned with. Further, exploratory laparotomy would aid in the resolution of the child's sex as well as make possible removal of an adrenal tumor if one were found. On this basis permission for laparotomy was requested from the parents and was granted. The child was operated upon by Dr. T. E. Chandler, to whom we express our sincere thanks. We quote directly from Dr. Chandler's report:

*May 10, 1938:* "This operation was made for the purpose of determining the sex of the child, and also with the idea of locating, if possible, the cause of her condition. Incision was made in the median line of the abdomen. Exploration was first made of the kidneys and no departure from the normal was found in either kidney. The pelvic parts were then examined. In the median line, extending upward from what seemed to be a normal sized cervix, was a cord about  $\frac{1}{2}$  cm. in diameter and enlarging to 1 cm. in diameter, about 2.5 cm. in length. It was flattened anteroposteriorly and was not more than  $\frac{1}{2}$  cm. in thickness. This was evidently a rudimentary fundus uteri. Springing from the cornua are normal tubes such as would be found in a girl of about her size with ovaries normal for her apparent age. Exploration was made of the canal of Nuck; no evidence of testicles was found here or in the labia. The wound was closed with layer sutures of catgut and stay sutures of silk worm gut.

*"May 19, 1938:* The sex of the child having been determined as that of a girl, with the consent of the parents an enlarged clitoris was removed. A circular incision was made about its base which was dissected up from attachments and the wound closed with sutures of catgut."

The determination of the child's sex as female eliminated one uncertainty in the interpretation of the data. At the present time we feel that hypergonadism and, equally, cortical tumor can be eliminated from the picture. The remaining condition, pituitary involvement, is not clearly defined although offering some supporting evidence. The more remote possibility, a pineal involvement, is also to be held in consideration. On the basis of probability the child has pituitary involvement. She will be studied at frequent intervals in the hope of resolving the matter within a reasonable period of time. Through the courtesy of the mother we were able to make a rather complete study of her. Elaborate analysis is omitted in the interest of economy of space. The general picture was one of normality, exhibiting solely an essential hypertension. Pelvic findings were devoid of features germane to the present matter. The serological findings, as well as the remaining picture, were normal.

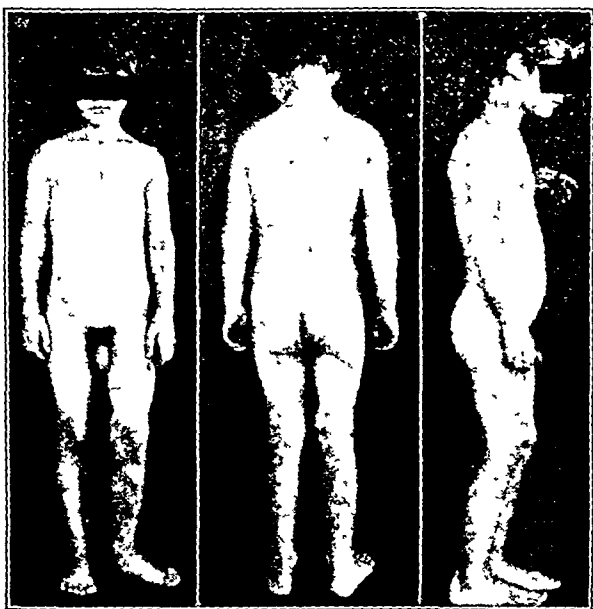
**CASE B-812 AND B-1008. PUBERTAS PRAECOX.** The case of this patient is reported as in some ways it parallels that of the preceding patient, although no doubt as to the sex existed. The patient was a  $4\frac{1}{2}$ -year-old boy with stature of a lad of nine, strong, muscular and vigorous, with large genitalia, well-grown pubic hair and other evidences of maturity. As his early puberty was of possible endocrine origin, he was submitted for the study to ascertain if possible its cause.

*Family History:* The patient is the second child of five, born in an interval of six years, to parents who were, respectively, 21 and 19 at the time of the patient's birth. At the time of the patient's admission the mother, at the age of 22, was far along in her sixth pregnancy. The other children and the father and mother are en-

tirely normal and nothing which bore on the case could be elicited concerning the grandparents.

*Past History:* While the mother was on her way to the hospital to be confined she met with an accident, but sustained no serious injury. The delivery was normal but delayed. The boy's first tooth appeared in the seventh month, he walked in the fifteenth, and talked at two years of age. He had whooping cough and chicken-pox. The history was otherwise not relevant. His large size and unusual genital development were first noticed at the age of one. As he has grown he developed a number of behavior problems which led to his reference to the Fernald School. Through the courtesy of Dr. Ransom Greene, to whom we express our sincere thanks, his records have

PLATE IV



Case B-812

been made available. His school comment on social history is: "Ego-tistical, quarrelsome, selfish, stubborn, seclusive, somewhat resentful of authority, a leader, difficult to control. Shows no affection for mother. Teases other children." His moral reactions: "Steals and hides things. Masturbates. Started fire in a tin pan. Developing delinquent tendencies." At the time of his first contact with the Fernald School his intelligence quotient was 93.

*Physical Examination:* The boy had the appearance of a well-developed and nourished lad of nine, of strong, sturdy build, the knee and ankle joints being especially large. The voice was of deep, male type, the genitalia of adult size and development with some pubic hair. Fine, light hair covered the face, neck and arms; that of the

head was thick, light and fine. There was a small amount of discharge in the nasal cavities. Twenty first teeth were present, those in front being widely spaced; several large cavities were noted. The tonsils were large, the thyroid was not palpable. The pulse rate was somewhat rapid, and there was a slight systolic murmur at the apex. Examination of the abdomen was somewhat unsatisfactory. The penis was 9 cm. long in a relaxed state; scrotum and testicles were of proportionate size. There was a slight tendency to spasticity in the legs, most noticeable in the adductor muscles, producing a peculiar type of gait. At times the patient experienced difficulty in voluntary separation of the legs. The routine neurological examination gave substantially normal findings.

*Laboratory Summary:* The boy was, by normal calculations, 19 per cent underweight, which is actually not the case, as his sitting height index was very high (.57); his lung capacity was about half that of prediction. The standards for the basal rate at this

PLATE V



Case B-812

age are not well defined. His observed rate in the best of a series of observations was 1058 calories. An independent measurement by Dr. Fritz B. Talbot, to whom the authors express their indebtedness, gave a value of 1145. Neither of these rates was probably quite basal. Comparison with the various standards show a range of from +39 per cent by the age standard to -22 per cent by Bailey's area standard. The several Talbot values are slightly higher than the lowest observed rate. The age value is patently meaningless and we felt in this case as in the one just discussed that the rate was either normal or slightly depressed. The blood pressure was low, urine volume low, protein intake slightly low, residual nitrogen fraction definitely high. The sugar tolerance was much depressed, the blood sugar slightly below the conventional normal. The blood morphology showed a slightly high red count and an increase in the endothelial leucocytes. A long series of blood pressure measurements showed an average of 96 systolic and 55 diastolic.

*Radiography:* The frontals and sphenoids were undeveloped; the sella was small with thick posterior clinoids. Hands, wrists and knees show the development of a 12-year-old boy. The mediastinal shadow was slightly enlarged. A gastro-intestinal series was entirely normal. At one of the earlier examinations it was thought that a mass could be demonstrated in the neighborhood of the right kidney. This was not confirmed by later examinations, but it was felt that the matter should be thoroughly investigated and a pyelogram of the right kidney was taken which gave entirely negative results.

*Cystoscopy* gave normal findings.

*Bilateral Ureteral Catheterization:* Normal function was demonstrated in both kidneys.

*Chest Examination* gave normal findings.

*Orthopedic Examination:* The examiner found evidence of heading at the costochondral sutures, suggesting an earlier possible rachitic condition.

*Nose and Throat Examination:* The tonsils were found to be hypertrophied and infected.

*Neurological Examination* gave normal findings.

*Abdominal findings* were normal.

*Eye Examination:* Owing to the patient's age the fields could not be demonstrated. Enlarged blind spots were detected by use of the Lloyd slate. Remaining findings were normal.

*Urea Index:* Value of 72, which implies a loss of permeability,

*Discussion:* This case, like the one previously discussed, gave evidence of a precocious puberty, the primary cause of which could not be completely ascertained by the study as given. The patient's low blood sugar, which was confirmed by several observations, and the consistently low blood pressure were suggestive of lowered adrenal function in which presumably the medulla would be primarily involved. On the other hand, the various genitourinary examinations argued against a cortical tumor of any magnitude. The lowered sugar tolerance, as has been shown by one of us, would be entirely consistent with an adrenal insufficiency. The mediastinal shadow could be interpreted in several ways, among which could be a persistent thymus. With the very dubious case for an endocrine activity of this gland it was felt unnecessary to consider this possibility as of primary significance. If there were an adrenal tumor its prompt removal was essential. On this basis permission for an exploratory laparotomy was received from the parents. The patient was operated upon by Dr. R. C. Wiggin, to whom the authors express their indebtedness. We quote:

"Under ether, operation was performed by making incision in the right semi-lunaris opening into the abdominal cavity. The intestines were pulled to one side and both kidneys palpated. There was no evidence whatsoever of tumor in either kidney, but I incised the posterior peritoneum and freed the kidney and examined the adrenal region on both sides. No disease was found. The peritoneum was then closed and a large appendix was removed by the cuff method. The wound was closed with catgut and silk worm gut."

With the adrenals probably eliminated, no evidence of testicular involvement, and the pineal and thymus of a very dubious endocrine activity, the pituitary remains as the most probable of the endocrine agencies concerned. The case was far from clear cut, however, as there were missing a number of findings of pituitary disease. That

the youth of the patient might be a factor in this was obvious but, lacking standards, interpretation became a matter of opinion. The little patient presented a considerable social problem. With a mentality on a parity with his age, a physique of a boy of nine, and adult sexual development, it was evident that the child would have to be safeguarded. Through the courtesy of Dr. Greene, and with the consent of the parents, the child was committed to the Fernald School with the understanding that he would be studied at six-month intervals in the hope that the trend would establish a diagnosis. The second study has just been completed (see B-1008). He has grown 8 cm. and increased 4.4 kgm. in weight. His weight is still 22 per cent below prediction, but the comment on the inaccuracy of the earlier standard still operates, the sitting height index being unchanged. His observed basal rate has increased disproportionately so that he is 64 per cent above his age prediction and but 13 below that of the area formula of Bailey. He is 6 per cent above the Harris-Benedict prediction. On this basis it seems to us possible that the interpretation of the earlier measurements was in error and that the predicted basal really lower than the higher value to which we gave the greater weight. This matter will be resolved as time goes on. The blood pressure has increased a little, the pulse is more rapid, CO, is diminished—this probably due to some incooperation on the part of the patient. The urine volume is now normal, but the urine shows both a very slight trace of albumin and a few hyaline casts. The rotein intake is better, the residual nitrogen much lower, though still above the normal. The sugar tolerance has increased but is still below the normal. Blood sugar is now in the normal range and the leucocytic formula is substantially as before, the actual number of the white cells, however, defining a slight leucocytosis.

*Radiography:* The hands, wrists and knees present the same picture as before, the sella is slightly larger with the thick posterior clinoids still present. The mediastinal shadow is somewhat smaller.

*Neurological findings* normal, as before.

*Nose and Throat Examination* shows the tonsils enlarged but less evidence of infection.

*Cardiogram* is normal.

*Eye Examination:* The eye grounds are still unobtainable. The discs are now reported as yellowish.

The present picture is somewhat more suggestive of a pituitary disturbance but again falls short of any real definition. The boy's behavior has improved and he showed a much larger measure of co-operation than at the time of the first study. During his first stay in the hospital he stole some matches and set his bed on fire. During his second stay, under the same degree of supervision, there were no overt acts. He had been reported to us as a bed-wetter but in neither of his hospital stays has this been in evidence.

The boy will be examined at intervals of six months. At the present time we feel warranted in reporting him only as unclassified, though there is some suggestion here of a possible pituitary involvement. Neither this case nor the one preceding is to be regarded as showing deviation of the endocrine function of the gonads. In fact, they certainly derive from other endocrine causes than the sex glands. Presenting, as they do, however, evidences of an early maturity which has frequently been classified as due to "hypergonadism," it has seemed worth while to discuss them for the negative value which they possess.

GROUP II. HOMOSEXUAL

**CASE B-408.** The patient gave as her chief complaint general fatigability, general lack of endurance and interest, and mental depression. The condition apparently dated back to puberty. At the age of 17 there was a nervous breakdown, and at the age of 32 a second and more severe attack, requiring committment to a sanitarium. After eight months' stay here the patient attempted suicide with a revolver. The bullet passed through the skull, inflicting seemingly no permanent serious injury. The patient developed homosexual tendencies which first found expression at about the age of puberty. There had been at least four distinct attachments, one of which was in progress at the time of her hospital admission. The patient assumed the passive role. After her suicidal attempt she convalesced in some measure from the mental condition and ultimately returned home. Her fatigability, however, increased, and for the last few months she has been incapacitated for any sort of physical exertion.

*Family History:* All the members of the family were somewhat highly strung. There was no history of disease conditions of significance.

*Past History:* The patient reported minor ailments, scarlet fever, a severe abscess on the left thigh, tonsillectomy at the age of 21, and other events noted above. She complained of frequent headaches, not relieved by glasses. The appetite was poor, bowels were regular. She established the catamenia at 15½; the flow was regular but distinctly scanty. She had always been much underweight. She disclaimed all interest in the male sex, acknowledged her homosexual tendencies, but stated that they were under complete control. This, like several other statements, was misleading.

*Physical Examination:* The patient was a slightly built, thin and undernourished woman in her mid-thirties. The hips were narrow and the general body configuration that of an adolescent boy. The head showed the scars of two bullet wounds, but was otherwise not remarkable. Teeth were in fair condition. There was a somewhat asymmetrical chest expansion; the breasts were small and undeveloped. Pubic hair was distinctly masculine in distribution and the legs showed hypertrichosis. Routine neurological examination gave normal findings.

*Laboratory Summary:* The patient was 29 per cent underweight and somewhat below her predicted lung volume. A fairly satisfactory basal rate was 13 per cent below prediction. The blood pressure was low and the CO<sub>2</sub> definitely below the normal. The urine volume was scanty, protein intake was inadequate, redissal nitrogen normal. Her sugar tolerance was 50 per cent below the normal. The blood showed a very marked lymphocytosis.

*Nose and Throat Examination:* The examiner demonstrated infected tonsillar remnants.

*Neurological Examination:* The examiner defined the condition as a manic depressive psychosis of the depressed type. There was no evidence of organic nerve lesion.

*Endermal Tests:* The patient gave a positive reaction to egg albumin.

*Radiography:* The skull showed the effects of the earlier trauma but was otherwise normal.

*Eye Examination:* The discs were yellowish, remaining findings normal.

*Discussion:* The clinical and laboratory study here point clearly to an ovarian failure. It was recommended that the patient have the infected tonsillar remnants removed, eggs omitted from the diet, and that endocrine therapy be followed. In view of her suicidal tendencies it was also recommended that she be placed under restraint.

A later report shows no real improvement in the condition, but glandular therapy was exhibited for only a short time.

**CASE B-530.** The patient was a delinquent girl of 19 with a history of hetero- and homo-sexuality, together with other sex perversions. She had also committed petty thefts and had presented other behavior problems. She had been committed at the age of 13, six years before her admission to the hospital. As she had become obese and had developed a number of possible endocrine stigmata, she was referred to this Clinic for study.

*Family History:* The patient was an orphan; there are a brother and sister who are entirely normal. The family history as recorded is not informative.

*Past History:* As a child she had minor ailments, removal of a . . . or from the left leg, tonsillectomy and adenectomy. She complained of an occasional headache, rather frequent nose-bleed for a short time a year previously, and recently had had an abscessed tooth. The menstrual history was substantially normal, with establishment at the age of 13.

*Physical Examination:* The patient was a very well developed, somewhat obese girl of 19. The hair on the vertex was coarse and thick. The eyes were normal; the thyroid not palpable. The hands and feet were large and symmetrical. There was a distinct flattening of the normal thoracic curve upward from the fifth vertebra. She had considerable acne on the face and chest and a minor inguinal adenopathy. The body hair was abundant but approximated the female configuration. A routine neurological examination gave normal findings. Mentally she was found to be rather slow.

*Laboratory Summary:* The patient was 23 per cent overweight. An unsatisfactory basal test was 5 per cent above prediction, her true rate being unquestionably lower. The blood pressure was slightly low, the temperature slightly high. Alveolar CO<sub>2</sub> was a low normal. The urine was normal throughout; the phthalein test slightly low; the sugar tolerance half the normal level. The blood was lymphoid in type.

*Pelvic Examination* showed an introitus admitting two fingers; otherwise the findings were normal.

*Barany:* Static labyrinth showed an almost total lack of response to stimulation. This was felt to be congenital as a growth or a toxæmia would not be likely to destroy the function of the static branch of the 8th nerve before beginning to affect the cochlear branch.

*Neurological findings* were substantially normal. A possible nystagmus was recorded.

*Radiography:* The sella was normal and the thoracic spine normal. One infected tooth was disclosed.

*Cardiogram* was normal.



*Eye Examination:* The right disc was slightly yellowish; remaining findings were normal.

*Discussion:* The general picture here presented suggests an ovarian failure. Ovarian medication was recommended and the patient discharged. Eighteen months later she was again admitted. In the meantime, so far as we could ascertain, she had received no medication. The laboratory picture which she presented was substantially identical with that first recorded. She had attempted to diet, but had lowered her weight by less than 2 lbs. Under wise direction and suggestion her social status had improved. Certain of the behavior problems had become less serious and she was definitely on the way to rehabilitation. She was discharged with the strong recommendation that she be given the benefit of endocrine medication. A later report records definite general improvement.

A point of interest in this and the preceding case is the persistence of a sex appetite, albeit abnormal, in the presence of ovarian failure. We have had occasion to remark this many times and in many women with wholly normal heterosexuality we have recorded a marked libido persisting for years after demonstrable ovarian failure. Extreme cases are those in which castration is the cause of the hypogonadism, and even here a loss of sex appetite is by no means the invariable rule. A male case in the next group is possibly significant in this connection.

#### GROUP III. CASTRATES

**CASE B-42.** The present case is particularly interesting as demonstrating the slight influence on the general picture which ablation of the testicles in adult years will produce. The patient had been operated upon eight years before for tuberculosis of the testicles by Dr. John H. Cunningham, through whose kindness and interest we were able to study this patient. At the time that the patient was 19 years of age he noted some irritation of the penis. There was a slight discharge and some burning on micturition. He was treated by several physicians for gonorrhea. Ultimately he consulted the referring physician, and the condition was diagnosed as a tuberculous state. One testicle was removed nine years ago, the patient being 25, and the second three months later. For some 15 years the patient has had a cough which is usually unproductive. He entered the hospital for a general survey and primarily, in a very gracious spirit of cooperation, to assist in the work of the Clinic.

*Family History:* The mother and two sisters died of tuberculosis; the remaining history not significant.

*Past History:* The patient reported measles and malaria, an earlier attack of jaundice, and the condition noted above. He had occasional attacks of vertigo, some obstruction of the right nostril, some loss of hearing in the right ear. He had a tendency to constipation and had lost about 20 lbs. since his operation. A tonsil and adenoid operation had been performed a year previously. The tuberculous condition had been apparently eradicated.

*Physical Examination:* The patient was well developed and somewhat underweight, the skin was somewhat dry, teeth showed much dentistry, breath sounds and vocal fremitus apparently somewhat increased on the right. Blood pressure was slightly low. The scrotum was empty. The knee jerks were reported as somewhat exaggerated and the cremasteric reflexes absent.

*Laboratory Summary:* The patient was 11 per cent underweight and the basal rate was 11 per cent below prediction. The somewhat low blood pressure was confirmed; the pulse rate and temperature were somewhat low. The urine presented an entirely normal picture. The phthalein output was normal. Sugar tolerance was normal. Blood constituents were normal. The blood showed a 4 per cent eosinophilia.

*Radiography* findings were normal throughout.

*Discussion:* At the time this patient was studied it was not possible for us to secure a number of the observations which have become routine in the later investigations. The significant feature of the laboratory picture is its relative normality, a borderline basal rate with somewhat low blood pressure being the only real departure from the normal. The subsequent history of this case is very striking and we believe worthy of record. At the time that the patient was seen his real difficulty lay in his profound mental depression. It was this condition rather than physical fatigability which had been progressively lowering his effort and lessening his ambition. After his operation he had returned to the small country town in which he had been born, giving up a varied and interesting career which involved

TABLE XIX

	Castrates				Mumps	
Case Number.....	B-42	S-197	S-261	S-1074	B-103	S-735
Sex.....	M	F	F	F	F	M
Age..... (yrs.)	34	42	59	68	20	40
Height..... (cm.)	169	164	167	160	155	175
Weight..... (kgm.)	52.9	60.7	62.8	51.8	47.0	66.9
Weight Deviation..... (%)	-11	+14	+18	-6	-12	-5
Lung Volume Deviation..... (%)	-7	-11	-20	-9	-25	+5
Basal Rate Deviation..... (%)	-11	-17	-15	-21	-13	-15
Blood Pressure..... (mm.)	106/62	120/82	128/52	124/62	104/72	106/58
Pulse Rate..... (per min.)	58	70	80	60	80	64
Temperature..... (deg. F.)	97.5	98.6	98.2	98.2	98.8	98.2
Alveolar CO <sub>2</sub> ..... (mm.)	41	35	34	40	32	44
Urine Volume..... (cc.)	1150	1050	960	2000	720	1360
Spec. Grav.....	1.022	1.014	1.020	1.015	1.012	1.018
Albumin.....	0	0	0	+	0	0
Casts.....	0	0	0	0	0	0
Sugar.....	0	+	0	0	0	0
Total Nitrogen..... (gms.)	10.64	7.13	11.07	11.85	8.46	7.28
Residual Nitrogen..... (%)	1.6	13.5	7.9	10.8	9.5	6.9
Phen. Sulph. Phthal..... (%)	58	64	57	60	58	53
Galac. Tol.—						
Normal..... (gms.)	30	40	30	30	40	30
Observed..... (gms.)	30	20	20	20	20	30
Deviation..... (%)	+0	-50	-33	-33	-50	+0
Blood—						
Non-Protein Nitrogen (mgm.)	34	30	42	32	31	34
Uric Acid..... (mgm.)	2.8	3.0	3.8	2.0	4.0	3.7
Sugar..... (mgm.)	82	91	91	84	76	90
Haemoglobin..... (%)	90	90	95	90	85	80
Erythrocytes..... (10 <sup>9</sup> )	5.52	6.07	4.84	5.07	4.58	4.72
Leucocytes..... (10 <sup>9</sup> )	9.10	8.60	5.25	4.30	5.50	5.20
Neutrophiles..... (%)	68	38	47	67	60	59
Lymphocytes..... (%)	23	56	43	25	32	34
Eosinophiles..... (%)	4	1	5	1	1	5
Monocytes..... (%)	5	5	5	7	7	2
Misc..... (%)	0	0	0	0	0	0

B-42 Male castrate (Tuberculosis of testicles).

S-197 Female, pre-menopause castrate before menopause age.

S-261 Female, pre-menopause castrate after menopause age.

S-1074 Female, post-menopause castrate after menopause age.

B-103 Oophoritis following mumps.

much foreign travel. He naturally resumed relations with the young people with whom he had grown up, and with his attractive personality and extremely interesting conversation he won the regard of one of the young women of the town. She was entirely willing to marry him, knowing in full his physical condition. Shortly after his visit to the hospital this plan was carried out. The patient found himself not only capable of erection but of intercourse with his wife which was entirely satisfactory to her. The psychological effect of this outcome was very striking. He resumed his outside interests shortly after his marriage, and moved to the West, where he organized and is conducting a most successful business in one of the larger cities. That the erectile power is not destroyed by castration after maturity is well known. This protocol is offered as a striking example both of the slight effect on the physical picture produced by castration, and the very definite influence on the patient's psychology produced by the conviction that a portion of his manhood remained in spite of his mutilating operation. The authors feel that a case such as this may explain some of the miracles which operative procedures are alleged to have wrought.

**CASE S-197.** This patient represents the results of castration in the pre-menopausal period studied before the menopause would normally have taken place. Her complaint on entrance was of failing vision in the right eye. She had suffered from this for the past six months. Since the initial onset of the condition there had been some improvement, but there remained an impression in her mind that the vision was circumscribed. Four years previously she had had a complete hysterectomy following which headaches from which she had previously suffered were improved. Three years previously she developed a feeling of soreness in the epigastric region, tenderness of the abdomen, and occasional vomiting spells.

*Family History* was entirely irrelevant.

*Past History:* The patient had mumps and chicken-pox in childhood, typhoid at 21, and scarlet fever 2 years ago. She has always had the headaches mentioned above. An examination of the eyes previous to her admission gave only normal results. She reported an occasional nose-bleed, recently some slight precordial pain, occasional slight palpitation. There was a tendency to constipation. The patient had been having hot flashes since her operation. The catamenia began at 14, was regular with diminished interval and somewhat profuse flow. There was continued flow for some six months prior to the operation which was necessitated by a fibroid tumor.

*Physical Examination* showed a well-developed and well-nourished woman; the skin was somewhat dry and wrinkled; there was slight lateral nystagmus in both eyes, not confirmed later, and slight epiphora; the majority of the teeth were missing; the tongue showed a slight tremor, the tonsils were enlarged but apparently not offending; there was a slight cardiac systolic murmur, tenderness in the iliac regions, and a few superficial varicosities on the extremities.

*Laboratory Summary:* The patient was 14 per cent overweight with a basal rate of —17 per cent and slightly low blood pressure. Alveolar CO<sub>2</sub> was low. The urine picture was normal except for the presence of a trace of sugar and a high residual nitrogen. Her sugar tolerance was half that of the uncastrated woman of her age. The blood constituents were normal. The blood was lymphoid in type.

*Radiography:* A gastro-intestinal series was normal. The shadow of the gall bladder was reported as slightly more dense than normal. The lungs showed some increased density.

*Eye Examination* showed a very slight enlargement of the blind spots and was otherwise normal.

*Discussion:* The patient presented a fairly typical picture of hypogonadism as we have come to recognize it by the study of female castrates. The blood pressure is a little high, but the patient is 42 years old and somewhat nervous. The basal rate and the sugar tolerance are at typical levels, while the low  $\text{CO}_2$ , as has already been noted, is a common finding in conditions depressing the activity of the ovaries. Subsequent to the examination the patient gave no evidence of gall bladder disease, suggested by the skiagram.

CASE S-261. This patient was castrated before the menopause and was examined by us after the age at which the menopause would naturally have occurred.

The patient's chief complaint was a marked fatigability. The condition dates back some 24 years in its onset, when the patient first began to exhibit a severe asthenia. Six years later a panhypertectomy was performed, the patient being 41 years of age at the time. Subsequent to the operation the asthenia increased and there were attacks of faintness and even of collapse. As the years have progressed these have become fewer in number and less severe. More recently she has developed some palpitation, tinnitus and vertigo.

*Family History:* The patient is one of ten children, seven of whom survive. One of the sisters has been studied in this Clinic and shown to be endocrinopathic (see Case B-37 in later "pluriglandular" paper). The family history was otherwise not remarkable.

*Past History:* The patient had measles three times in childhood, mumps at the age of 15, the operation already noted, and a submucous turbinate resection and a hemorrhoidectomy. She had severe headaches for a number of years, but recently they have been infrequent. She reports an abscess in the right ear 15 years ago. She was subject to head-colds. The teeth have caused a great deal of trouble. She complained of hoarseness and an irritating cough. She was subject to urinary frequency and, when unable to void, to incontinence. The catamenia was established at 13, the periods were regular and flow very profuse. Of late years she has been troubled with vulval pruritus.

*Physical Examination:* The patient was a well-developed, somewhat obese woman of 59; the hair was dry and scanty and the scalp showed areas of eczema. The skin was dry and there were certain pigmented areas on different parts of the body. The remaining examination showed only a slight cardiac irregularity.

*Laboratory Summary:* The patient was 18 per cent overweight. The basal rate was —15 per cent. The diastolic blood pressure was definitely low, the systolic slightly so, the pulse was somewhat rapid. Alveolar  $\text{CO}_2$  was below the normal. The urine was negative. Nitrogen partition was normal. The sugar tolerance was at the pre-pubertal level of 20 grams. The non-protein nitrogen of the blood was above the normal. There was a definite lymphocytosis and a 5 per cent eosinophilia.

*Eye Examination:* Entirely normal.

*Radiography:* The skull was somewhat thick, the frontal sinuses obscured. There was an atheroma of the aortic arch and some pulmonary fibrosis. Remaining findings were normal.

*Skin Examination* defines seborrhea, eczema of the scalp and senile changes in the skin.

*Barany:* This test gave evidence of slight irritation, possibly toxic in origin.

*Neurological Examination:* No evidence of organic nerve lesion was secured. The patient was highly neurotic.

*Discussion:* The picture here conforms in significant findings with those to be predicted from a complete castration.

CASE S-1074. This patient represents a study of a woman castrated a number of years after the menopause. Her chief complaint was of eczema which involved the hands but no other parts of the body. This condition had obtained for a number of years, being more marked in the winter time and much better in the summer. The patient stated that she washed her hands fifty times a day in plain water and three times daily with a medicated soap.

*Family History:* Both the parents were arthritic. The mother died of cancer and a paternal uncle was psychotic. The patient was an only child.

*Past History:* She had the minor ailments in childhood, scarlet fever at 26 without sequelae, and was subject to a severe dysentery every summer during young girlhood. Fifteen years ago she developed a cardiac condition which necessitated her remaining in bed for three months. Twelve years previously she had had an appendectomy, and within the year a pan-hysterectomy had been performed for a large fibroid tumor, the patient then being 67 years of age. She complained of occasional headache, a long-standing post-nasal catarrh; she had had a submucous turbinate resection 25 years before, removal of several abscessed teeth and had one tooth still discharging. During young girlhood she was constipated, and has had a tendency to this condition throughout her life. The menstrual history was entirely normal, including an uneventful menopause at 50.

*Physical Examination:* The patient was an elderly woman seemingly in good physical condition and good nutritional balance. The teeth showed much dentistry; the nipples were undeveloped, there was a reduplication of the first heart sound, both kidneys were low, the right kidney movable, hands showed evidence of eczematous involvement, and there was some anterior curve to the dorsal spine, but the station and gait were very good for one of the patient's age.

*Laboratory Summary:* The patient was 6 per cent underweight. The basal rate was —21 per cent, with relatively a somewhat low blood pressure. The CO<sub>2</sub> was normal. The urine volume was ample, the urine contained albumin. The residual nitrogen was high. The sugar tolerance was at the prepubertal level of 20 grams. Blood constituents and blood morphology were normal. A long series of endermal tests showed the patient not reactive to a large number of proteins.

*Cardiogram* was normal.

*Radiography:* The heart was not enlarged; the sinuses and skull were normal; the teeth showed no infection, but there were numerous

bulbous roots consistent with exostoses. The lungs showed increased density and fine mottling at the apices.

*Chest Examination:* Normal findings were reported.

*Eye Examination:* There was an undefined central scotoma in the left eye which the examiner believed was due to retinal hemorrhage. Remaining findings were normal.

*Discussion:* The picture here presented is that of a woman of 68 in surprisingly good general physical condition. The lowered basal rate and sugar tolerance are the only real indices of endocrine disturbance. The probability would seem to be that during the years which had elapsed since the menopause (18), the patient had so far adjusted that her subsequent castration did not produce such marked changes as are normally observed in younger women.

#### GROUP IV. GONAD FAILURE FOLLOWING MUMPS COMPLICATED BY GONAD INVOLVEMENT

CASE B-103. OÖPHORITIS. The patient's chief complaint was of abdominal pain over the ovarian region. A few weeks earlier she had had an attack of the mumps and since her convalescence had become markedly asthenic and nervous. The pain was greater over the right ovary region, but there was a steady dull ache over the entire lower abdomen.

*Family History:* The mother and aunt had had pulmonary tuberculosis. One sister had some condition, the nature of which was unknown to the patient, involving the cervical lymphatics.

*Past History:* In addition to mumps the patient had had chicken-pox, measles and pertussis. Eight years previously, at the age of 12, the appendix had been removed and there was a partial resection of a cystic right ovary. The patient matured in the following year, and her subsequent menstrual history has been entirely normal. The remaining history showed a marked constipation, a sensitivity to fish, and a vaginal discharge for the preceding two years.

*Physical Examination:* The patient was a well-developed but somewhat undernourished girl of 20. The parotid and submaxillary glands were somewhat hypertrophied and tender. She had a slight bilateral nasal obstruction. The breasts were of the prepubertal type. Marked hypersensitiveness was elicited over both ovaries, more pronounced on the right. Hair was abundant but normal in distribution.

*Laboratory Summary:* The patient was 12 per cent underweight and 13 per cent below her predicted lung volume. The blood pressure was low and the  $\text{CO}_2$  definitely below normal<sup>1</sup>. The urine was somewhat scanty, otherwise normal. The residual nitrogen fraction was high. The sugar tolerance was half the normal. Blood uric acid was somewhat high, blood sugar slightly below normal. The blood morphology was normal.

*Radiography:* The skull and chest were normal. There was no evidence of sub-sternal enlargement. The barium enema disclosed no disorder of the colon.

*Neurological Examination* disclosed no evidence of any organic neurological condition.

*Bacteriological Examination:* The vaginal smear showed no pathogenic organisms.

*Pelvic Examination:* Reported as normal except for tenderness as already noted.

*Discussion:* The picture presented here is typical of gonad failure. The coincidence of the patient's mumps and the development of her symptoms would make it probable that an oöphoritis complicating the mumps was responsible for the lowered functional activity. Ovarian medication was recommended. A recent report states that the patient improved definitely, later married, and has two children. Our study here was of an acute condition which has certainly been corrected—probably as the outcome of natural curative agencies.

CASE B-457. The patient's chief complaint was of fatigability and asthenia, with occasional periods of extreme mental activity. He also complained of headache and insomnia. He had had orchitis at the age of 15 following a severe attack of mumps. He entered college at 19, but found it difficult to carry on his academic work because of fatigability. He stated that by concentration he was able to work very rapidly, but only for a brief space of time. He dropped out of college in the middle of his second year at the suggestion of the authorities. Since that time he had tried a variety of employments, in all of which he had failed. Shortly after leaving college he had a fall down an elevator shaft; was in bed for a month and incapacitated for work for six months. The fall produced only muscular injury. He reiterated a symptom of a feeling of pressure in the head, and to this he ascribed most of his difficulties. He also had suffered greatly from insomnia and had taken large quantities of various hypnotics to produce sleep. He had had extensive medical contacts and on several occasions had taken somewhat promiscuous endocrine therapy.

*Family History:* The patient was an only child. On the paternal side of the family are numerous neurotics; the father is himself extremely nervous and irritable.

*Past History:* The patient reported mumps as above, measles and whooping cough, the injury to the back already noted, a streptococcus infection of the neck 13 years earlier, a tendency to bronchitis, and for the last 30 years hay fever during the ragweed season. He complained of attacks of acute indigestion and of constipation. He gave a history of nocturia and a feeling of bladder irritation.

*Physical Examination:* The patient was a well-developed and fairly well-nourished man of 40. We quote from the examiner's record: "It was very difficult at first to elicit definite information. The patient seemed to have a very much retarded psychomotor activity and found it very difficult to remember things. He seemed very sleepy and would apparently fall off to sleep at intervals in the questioning. As the examination progressed, however, he became brighter and more alert, and at the end of about two hours became much aroused and excited over his general condition." The hair on the vertex was thin; the teeth were poor and showed much dentistry; heart action was slow but regular; the left testicle was the size of a large egg, the right slightly smaller; the knee jerks were hyperactive.

*Laboratory Summary:* The patient was 5 per cent underweight; his basal rate was —15 per cent; blood pressure somewhat low. The urine was normal, as was nitrogen partition. Sugar tolerance was

normal. Chemical blood constituents were normal. Blood morphology study showed a slightly low haemoglobin, a slight relative lymphocytosis, and a 5 per cent eosinophilia, undoubtedly referable to his hay fever.

*Radiography:* The chest was normal, as was the sella; large sphenoid cells were noted.

*Audiogram:* The aural acuity was normal.

*Neurological Examination:* The patient had been defined elsewhere as a psychoneurotic. The examiner found no evidence of organic nervous disorder.

*Eye Examination:* The disc margins were indistinct and the discs themselves were yellowish. The blind spots were slightly enlarged.

*Discussion:* In general the patient presented a normal picture. His nervous instability induced a lack of cooperation which prevented the performance of a number of desirable tests. Among these was a . . . . . The patient was not entirely ingenuous, . . . . . r massive detail in regard to his presenting . . . . . nsatory reticence about such matters as his sex life. The laboratory picture which he presented is identical with that produced by castration of the male in adult years. In the light of present knowledge we are not prepared to ascribe his nervous instability to this condition, preferring to regard the two as existing coincidentally.

TABLE XX

Case Number.....	Sterility		Normal Pregnancy			
	S-837	M-S	M-8		M-9	
Time.....	—	early	late	early	late	
Parous.....	0	1		3		
Age..... (yrs)	22	20	29	34	35	
Height..... (cm)	162.0	157	157	177.5	177.5	
Weight..... (kgm)	57.8	55.2	61.1	88.7	92.6	
Weight Deviation.. (%)	+1	+6	+23	+21	+32	
Lung Volume Deviation.. (%)	-31	—	—	-15	-7	
Basal Rate Deviation.. (%)	-9	+3	-6	-7	-5	
Blood Pressure..... (mm)	92/60	91/70	102/71	108/66	109/30	
Pulse Rate..... (per min)	72	90	88	70	80	
Temperature..... (deg F)	98.0	98.2	98.1	97.0	97.9	
Alveolar CO <sub>2</sub> ..... (mm)	11	36	33	35	34	
Urine Volume..... (cc)	520	910	1500	1200	3300	
Spec. Grav.....	1.033	1.021	1.015	1.016	1.010	
Albumin.....	0	+	0	+	0	
Cast.....	0	0	0	0	0	
Sugar.....	0	0	+	0	0	
Total Nitrogen..... (gms)	7.28	6.23	7.42	9.26	9.65	
Residual Nitrogen..... (%)	8.0	7.4	9.1	4.6	4.7	
Phen. Sulph. Phthal..... (%)	62	—	—	—	—	
Galac. Tol.—						
Normal..... (gms)	10	40	40	40	40	
Observed..... (gms)	< Normal	30	20	30	20	
Deviation..... (%)		-25	-50	-25	-50	
Blood—						
Non-Protein Nitrogen..... (mgm)	26	—	—	28	28	
Uric Acid..... (mgm.)	3.1	—	—	3.5	3.5	
Sugar..... (mgm.)	86	100	100	100	91	
Haemoglobin..... (%)	85			85	75	
Erythrocytes..... (10 <sup>6</sup> )	4.21			4.25	3.98	
Leucocytes..... (10 <sup>3</sup> )	5.80			8.80	8.30	
Neutrophils..... (%)	61	Recorded as normal		70	63	
Lymphocytes..... (%)	38			22	32	
Eosinophiles..... (%)	0			1	0	
Monocytes..... (%)	1			7	5	
Misc..... (%)	0			0	0	



GROUP V. STERILITY

CASE S-837. The patient's chief complaint as presented was a decalcification of the teeth. The condition had obtained for the last six months and the patient had been urged by her dentist to have the cause of the condition investigated. An additional factor was a sterility which the patient hoped to overcome. She had been married for something more than two years without conceiving. By inference, at least, the husband had been eliminated from the etiologic equation.

*Family History* was entirely irrelevant.

*Past History:* The patient had had minor ailments, influenza at the time of the epidemic, and a tonsil and adenoid operation at the age of 7. For the past few years she had suffered from frontal headaches. The catamenia began at 14, had always been irregular, with increase in the interval, while the flow was definitely scanty. The remaining history as given was not informative. The patient was distinctly egocentric, irritable, and incooperative, which naturally were matters of record and not of the patient's report.

*Physical Examination:* The patient was a well-developed and well-nourished woman of 22. There were a small sebaceous cyst on the right side of the vertex, a few palpable anterior cervical glands, a slightly enlarged thyroid. The remaining examination was not significant.

*Laboratory Summary:* The patient was within one per cent of her predicted weight. The basal rate was reported as —9 per cent, but the conditions of the test were not entirely satisfactory and the true value was undoubtedly somewhat lower. The blood pressure was low. Alveolar CO<sub>2</sub> was normal. The urine was scanty and concentrated, the protein intake somewhat low, the residual nitrogen fraction normal. Blood chemistry was normal. The blood showed a slight secondary anaemia and a relative lymphocytosis. The patient did not complete the sugar tolerance test, but the partial examination showed it to be below the normal.

*Pelvic Examination:* This had been performed elsewhere and was reported as normal.

*Blood Calcium:* The test showed 11.5 mgm., a slightly high value.

*Discussion:* The preparation of the case was patently incomplete. It was felt, however, that the picture was generally suggestive of a primary ovarian failure. Ovarian medication was recommended, and this was followed out. Within a comparatively short time the patient became pregnant and was later confined of a normal child. We are not informed as to the subsequent condition of the teeth, since contact with the patient was lost.

In a series of gonad failures which we have investigated a number of the subjects have given a history of sterility. During the earlier studies it was impossible to resolve this question satisfactorily, but more recently a clinic has been established for the specific study of this condition. Preliminary notices of the work have already appeared (56) and the results of the investigation will be reported elsewhere. In brief, it involves a very thorough clinical and laboratory study of both partners. The case recorded above illustrates the apparent correction of a sterility occurring more or less fortuitously, as the study of the patient was most incomplete and there were no available data for the male other than a general statement.

## GROUP VI. NORMAL PREGNANCY

The status of ovarian function during pregnancy is a moot point and has already been touched upon in an earlier portion of this paper. For a number of years past one of us has been conducting somewhat extensive studies on the laboratory and clinical findings during the progress of normal pregnancy. The data from two such cases are offered here as a text for general discussion.

CASE M-8. This patient was a woman of 29 who had been married for several years and who had just become pregnant. Through the courtesy of the patient's physician and her own gracious cooperation we were able to make repeated studies at intervals of substantially two weeks, during the last twenty-six weeks of the pregnancy. Two typical protocols have been selected and the laboratory data incorporated in the table above. These may be briefly reviewed. The patient was a young woman of 29, in good general physical condition. The family history was not significant; her own past history showed no important departures from the normal, and the physical findings were substantially normal. At the time of the first examination, which was twenty-six weeks before delivery, she was 6 per cent overweight, with a basal rate reported as +3 per cent. This latter was probably slightly high, as a week later she gave the value of -5 per cent. The blood pressure was low, pulse somewhat rapid, alveolar carbon dioxide a low normal value. The urine was a low normal in volume and contained a trace of albumin. Her protein intake was below a maintenance level, as gauged by the amount eliminated. The residual nitrogen fraction was normal. Her sugar tolerance was 10 grams below prediction. Of the blood constituents only the sugar was determined, the level obtained being normal. The blood morphology was investigated elsewhere and was reported to us as normal.

The second report was secured some two weeks before delivery. The patient had increased nearly 9 kgm. in weight and was now 23 per cent above prediction. The basal rate was -6 per cent, the blood pressure higher, but still at a hypotensive level. The pulse remained somewhat rapid. The  $\text{CO}_2$  had dropped to a level below the normal. The urine volume was ample, albumin had disappeared, but a trace of sugar was recorded. It may be said, parenthetically, that a slight glycosuria is frequently recorded during the course of pregnancy. The protein intake had apparently improved slightly, but was still at a sub-maintenance level. The residual fraction was just above the conventional normal. Her sugar tolerance had dropped to 20 grams, the level of prepubertal years, of castration and of severe functional failure. Again only the blood sugar was recorded, and that at the same normal level. The blood morphology was again reported as normal. Discussion of this case will be postponed until the data of the second case have been considered.

CASE M-9. In the study of this case we were peculiarly fortunate, as we had records of the patient's functional level prior to conception and were enabled, through her cooperation, to carry out a continued study throughout the entire course of her pregnancy. The data secured before conception showed a moderate degree of obesity (+14 per cent), a normal basal rate with normal  $\text{CO}_2$ , a normal blood and urine picture, and a sugar tolerance at 40 grams, the normal level for a healthy woman of her age in a state of sexual rest. The first test recorded in the table was secured in the thirtieth week before delivery. The patient had increased in weight materially and was

24 per cent above prediction. The basal rate was —7 per cent, the blood pressure somewhat low, the alveolar carbon dioxide at a low normal level. The urine picture was substantially normal, except for a very slight trace of albumin, an observation of frequent occurrence in this condition. The sugar tolerance was 25 per cent below prediction. The blood composition was normal, the blood morphology indicating a slight anaemic tendency. The leucocytic formula was normal. The last test was performed during the third week before delivery. The patient had added nearly four kgm. to her weight and was now 32 per cent above prediction. The lung volume had improved, a rather usual occurrence, as has already been noted by one of us (44). The basal rate deviation was —5 per cent, the blood pressure still lower than before, the alveolar carbon dioxide slightly lower. The urine volume had increased and was in excess of three liters. The remaining findings were entirely normal. The sugar tolerance had fallen to the characteristic 20-gram level, the blood composition continued normal, the anaemia was somewhat more pronounced. There was an absolute increase in the lymphocytes, which, however, were within normal limits.

*Discussion:* The basal rate changes during pregnancy have already been recorded by one of us (22) in a series of cases, and the findings have been confirmed in substance by careful studies on individual patients. During the early stages of pregnancy there is a tendency for the basal rate to fall somewhat below prediction, while the terminal phase reaches a level about the same amount above. Both values (—8 to +8 per cent) fall within conventional normal limits. The curve of change, however, in any given case shows considerable variation in the individual measurements. As earlier noted (23) Sandiford has suggested that this increase depends upon the added surface caused by foetal growth. As this assumption involves uncertain extrapolations and is based upon the study of a single case, too much weight should not be given to it. The fact remains, however, that for some cause not yet clearly determined, the basal rate increases during pregnancy an average of 16 per cent above the prediction based upon the usual conventional standards. This increase will obscure any lowering of the mother's individual basal as dissociated from that of the highly active protoplasmic mass of the foetus. A lengthy discussion may not be undertaken here. It may be said, however, that if allowance be made for the superimposed effect of pregnancy with its unknown mechanism, the maternal basal rates are not inconsistent with the slight depressions incident to ovarian failure.

The lowering of the alveolar carbon dioxide without any evidence of an existing acidosis parallels exactly the frequent observation in ovarian failure. The glycosuria of pregnancy (and this is a glycosuria, as has been clearly demonstrated) corresponds with the similar phenomenon observed in numerous other conditions, among which primary ovarian failure is numbered.

The lowering of the galactose tolerance parallels exactly the changes produced by the mild and by severe functional failure and castration.

To summarize then, the laboratory picture presented by the pregnant woman parallels closely that of non-pregnant female exhibiting a lowered endocrine activity of the ovaries. We do not feel that the case is proven, as it is recognized that pituitary changes take place during this interesting physiological event. With marked posterior lobe overactivity, however, the tolerance should sink below 20 grams, which in our somewhat extended experience has never been the case. Furthermore, the tolerance lowering appears very early

in the pregnancy and at a time when profound changes of pituitary activity are neither demonstrable nor probable. Teleology would support the general thesis. We offer the observed facts and a possible interpretation which we regard as probable but certainly not established.

TABLE XXI

	Psychosis				Deaf	
	1	2	3		4	5
Case Number	B-621	B-371	S-111	S-1051	S-1690	S-813
Sex	F	F	F	F	F	F
Age (yrs)	28	36	21	23	20	29
Height (cm)	155 6	159 3	158 0	158 0	163 0	150 0
Weight (kgm)	37 3	56 1	55 2	62 9	56 5	37.5
Weight Deviation (%)	-30	-6	+2	+11	+1	+9
Lung Volume Deviation (%)	+26	-6	-19	-5	+9	-20
Basal Rate Deviation (%)	-22	-19	-11	-11	-12	-14
Blood Pressure (mm)	98 60	100 62	98/72	112/68	90/18	100/61
Pulse Rate (per min)	76	70	76	74	70	68
Temperature (deg F)	98 4	97 5	98 7	98 1	98 8	98 2
Alveolar CO <sub>2</sub> (mm)	36	40	31	40	30	41
Urine Volume (cc)	1310	510	2130	1500	1090	710
Spec. Grav	1 015	1 021	1 011	1 016	1 017	1 019
Albumin	0	+	0	0	0	0
Casts...	0	0	0	0	0	0
Sugar	+	0	0	0	0	0
Total Nitrogen (gm%)	6 56	6 00	11 36	8 20	11 00	6 14
Residual Nitrogen (%)	13 5	9 5	13 5	8 9	8 1	11 2
Phen Sulph Phthal (%)	65	61	65	56	57	45
Galic Tol—						
Normal (gms)	40	40	40	40	40	40
Observed (gms)	20	30	20	20	20	20
Deviation... (%)	-50	-25	-50	-50	-50	-50
Blood—						
Non-Protein Nitrogen (mgm)	29	33	32	26	31	31
Uric Acid (mgm)	4 1	2 9	—	2 7	3 3	3 7
Sugar (mgm)	70	90	100	80	100	95
Hæmoglobin (%)	90	75	95	70	96	80
Erythrocytes (10 <sup>6</sup> )	1 98	1 03	5 62	3 80	5 61	4 71
Leucocytes (10 <sup>3</sup> )	11 50	5 25	9 80	6 80	7 60	11 80
Neutrophiles (%)	66	51	61	51	56	60
Lymphocytes (%)	29	12	32	39	12	29
Eosinophiles (%)	1	1	1	2	1	2
Monocytes (%)	1	3	6	8	1	7
Misc (%)	0	0	0	0	0	2

## GROUP VII. PSYCHOSES

The possible association of mental disease with endocrine imbalance is probably more generally accepted in connection with changing gonadal activity than in any other potential endocrine manifestation. The puerperal psychoses, the existence of which, it is true, is denied by many, the involution psychoses of the menopause, and possibly other types of mental disturbance appearing concomitantly with evidence of disturbed ovarian function, are cases in point. As we have discussed certain psychotic conditions appearing coincidentally with aberrations of both the pituitary and the thyroid, it seems appropriate to review a few of these cases in which a psychosis and a primary gonad failure occur concurrently.

CASE B-621. The patient was admitted to the clinic offering as a chief complaint epileptic seizures accompanied by vague abdominal distress. The history of the epilepsy dated back 21 years, at which time the patient was 7 years of age. She had had scarlet fever during this year, but the seizures had already manifested themselves prior to this event. Up to the time of the catamenia, which occurred

at 13, they came at substantially monthly intervals. Since that time they have come at irregular periods, the quiescent interval, however, tending to be greater than in the early years. The abdominal condition had developed only a few months previously and apparently was wholly independent of the epileptic attacks. She described this condition as a definite pain at the left of the umbilicus and which radiated upward. It varied greatly in severity and in the duration of the attacks.

*Family History:* The patient has one brother who is normal and healthy. The family history is entirely irrelevant.

*Past History:* The patient reported the minor ailments of childhood, scarlet fever at 7, as noted above; a tonsillectomy and adenectomy and an appendectomy. Some years before admission she attempted to commit suicide by drinking iodine, and in addition to this there were two later psychotic episodes requiring restraint in an institution. She reported severe headaches with her epilepsy during the earlier years only. She was subject to palpitation, was constipated and complained of frequent attacks of indigestion. The menses were established at 13 and were regular but somewhat scanty. She has always been much underweight. The girl was a very simple-minded, immature individual whose presenting difficulty had caused a marked degree of isolation. Her life was very narrow and her mother, her sole associate. There has been a constant fear in later years that the mother would die and leave her alone, in which event she planned to die also.

*Physical Examination:* The patient was a fairly developed but much undernourished woman of 28. The lips were slightly bluish, the teeth in poor dental repair and several missing. The breasts were small and somewhat undeveloped; the heart, lungs and abdomen were normal, the knee jerks were hyperactive, and the remaining findings substantially normal.

*Laboratory Summary:* At the time of examination the patient was 30 per cent underweight, but definitely above her predicted lung volume. The basal rate was —22 per cent, the blood pressure definitely low, CO<sub>2</sub> a low normal. A trace of sugar was recorded in the urine, which was otherwise negative. The protein intake was below a maintenance level. The residual nitrogen fraction was very high. The sugar tolerance was half the normal. Blood uric acid was high and blood sugar low. There was a slight leucocytosis and a normal leucocytic formula. A report from the Boston Psychopathic Hospital,\* made three years earlier, showed comparable values for the blood and urine findings and a basal rate very much higher. This latter was undoubtedly not the patient's true level. A second report from the Psychopathic Hospital of an admission a few months earlier than her admission here was again confirmatory as to the blood and urine findings. The basal rate was much lower than before, but still above prediction, and undoubtedly not representative of the patient's true basal rate.

*Nose and Throat Examination* gave normal findings.

*Radiography:* The heart, lungs, skull, sinuses and sella were all normal. The teeth showed no focal infections, but one retained root was demonstrated. A gastro-intestinal series was normal.

*Neurological Examination:* The examiner found no evidence of organic disease. He defined the condition as a true epilepsy.

\*We take much pleasure in acknowledging our indebtedness for this and many similar courtesies.

*Pelvic Examination:* The patient showed a somewhat excessive hair growth; the examination was otherwise not informative.

*Eye Examination* showed slightly enlarged blind spots, but otherwise no abnormality.

*Spinal Fluid* was reported to us as normal.

*Intelligence Quotient* was reported to us as 86.

*Discussion:* At the time of the first admission to the Psychopathic Hospital she was discharged with a diagnosis of psychosis with epilepsy. Re-examination a few months before her entrance to this Clinic disclosed epilepsy without psychosis. The laboratory picture here presented by the patient was consistent with a primary ovarian failure, and she was discharged with the diagnosis of hypogonadism with epilepsy. The question of existing psychosis was left in abeyance. Under the direction of one of us she was treated with follicular hormone and in a few weeks her general condition had improved materially. The basal rate had become —10 per cent, the blood pressure had increased to 106, the sugar tolerance was normal at 40 grams, the blood uric acid had fallen to 3.3, and the blood sugar increased to 91 mgm. She still showed high residual nitrogen in the urine. In so short a space of time it was impossible to say what influence this improvement of her functional level could have on her major difficulty. Her general condition was certainly improved at the time of her admission for the second study.

CASE B-374. The patient's chief complaint as given by herself was indigestion, from which she had suffered for about three years, with pain apparently both in the stomach and the abdomen, though the patient's description was not clear cut. Two years previously she had been for nearly a year at the Boston Psychopathic Hospital and been discharged as unimproved, with a diagnosis of dementia praecox. The first mental deviation was noted at the age of 18 by her family, when she began making remarks which were in nowise germane to the situation or to current conversation. Subsequently she graduated from college, making the Phi Beta Kappa. Following graduation, she taught in several high schools, but a gradually increasing repugnance to this work led her to discontinue it after two or three years. She was decidedly erratic during this period. She then took a course in a business college and subsequent to this was employed in a variety of business positions, including some newspaper work. She was not successful in any of these endeavors, and ultimately she went into the missionary field. Here erotic tendencies developed and she was brought back to Boston and placed in the Psychopathic Hospital, where she remained for about a year, as noted above. From that time until her entry into this Clinic, some  $2\frac{1}{2}$  years later, she had remained with her family, showing steady downward progress in the trend of her psychosis.

*Family History:* The patient was one of a large family, the general history of which was not significant.

*Past History:* She reported only minor ailments, an earlier otitis media and an occasional headache. The bowels were irregular. The menstrual history was not remarkable, except for very scanty periods. The remaining history was not significant, and in some respects was independent.

*Physical Examination:* The patient was a well-developed and nourished woman of 36, oriented as to environment and time. The

hair was normal in amount and distribution. The face showed a marked degree of brownish pigmentation, simulating the "mask of pregnancy." The breath was foul, the teeth in fair condition only. Fusiform papillae on the anterior two-thirds of the tongue were very prominent and the glossal margin showed numerous teeth impressions. There was no thyroid enlargement. The remaining examination, including routine neurological observations, was not informative.

*Laboratory Summary:* The patient was 6 per cent underweight. The basal rate was 19 per cent below prediction, with very low blood pressure. The urine volume was scanty; albumin was recorded. The protein intake was apparently below a maintenance level; the residual nitrogen fraction was high. The sugar tolerance was 25 per cent below the normal. The blood was lymphoid in type; there was a 4 per cent eosinophilia and a secondary anaemia.

*Eye Examination:* The patient showed some symmetrical contraction of form and color fields.

*Neurological Examination:* The examiner defined a psychosis, probably a dementia praecox.

*Radiography:* Gastro-intestinal examination disclosed no abnormalities, except for probable disease in the appendix.

*Pelvic Examination* disclosed no abnormality.

*Bacteriological Examination:* A vaginal smear was normal.

*Discussion:* The general picture here is consistent with ovarian failure. The erotic element in the patient's complex is entirely consistent with this condition, as has been recorded elsewhere in this paper. That the psychotic condition is directly connected with the endocrine state is not a supportable thesis with such information as we have at present. Ovarian therapy was recommended, together with the necessary steps to correct existing difficulties, such as the anaemia and the pathological appendix. The subsequent history of this case is unknown to us.

CASE S-411 AND S-1054. The patient gave her chief complaint as a nervous breakdown. The more complete history was received through the courtesy of the referring physician, who stated that the patient had a brief psychotic attack prior to 1922, from which she recovered spontaneously. Again early in that year there was a period of depression which led to her commitment to the Boston Psychopathic Hospital, from which she was transferred to the Wiswall Sanitarium in February. The patient was excited, noisy and destructive and required occasional tube feeding. She remained in this condition for several months. There was a gradual diminution of the excited phase, with brief recurrence at the time of her periods. She gradually declined into an apathetic state and five months after her admission she cleared very rapidly, and in July of 1922 was sent home on a trial visit. She was readmitted on May 7, 1923, having lived an entirely normal life up to within a few days of her admission. She went through substantially the same cycle and was sent out on November, 1923. In May, 1924, she was again admitted, ran the same course of symptoms, and was sent home in September. The diagnosis established was that of a manic depressive psychosis. She was admitted here for study in late September of 1924.

*Family History* was not relevant. The patient is one of six children.

*Past History:* She reported measles, scarlet fever and chicken-pox in childhood. The remaining history was entirely irrelevant, including that of the catamenia.

*Physical Examination:* The patient was well developed and nourished, the eyelids were inflamed, teeth were irregular and showed many fillings, there was a possible slight thyroid enlargement, the breasts were small and undeveloped, there was much hair on the chest and legs, and the pubic hair assumed the male configuration. The remaining findings were normal.

*Laboratory Summary:* The patient was within 2 per cent of her predicted weight. The basal rate was —11 per cent, blood pressure definitely low, CO<sub>2</sub> substantially below the normal. The urine volume was large, protein intake high, residual nitrogen much above the normal. The sugar tolerance was half the normal. Blood chemistry and blood morphology were substantially normal.

*Neurological Examination* gave no evidence of organic nervous disease.

*Discussion:* The patient presented a clear-cut picture of ovarian failure, with practically all of the evidences which we have learned to associate with this condition. Ovarian medication was advised.

Eighteen months later the patient was returned to us for further study. There had been one additional attack which had run the same course as the earlier seizures. She had had a series of boils in the preceding winter; the remaining history was not striking. She stated, however, that she had been under osteopathic and chiropractic treatment and had not followed the endocrine medication. The physical examination confirmed the earlier findings. There was, if anything, an increased hair growth, the external genitalia were essentially female in character and well developed. The recorded blood pressure was low. Laboratory examination showed an increase in weight of nearly 8 kgm. The basal rate was —14 per cent, the blood pressure at this time was higher than that recorded by the House Officer, but still low; the pulse was normal, as before. The urine volume was now more nearly normal; her protein intake had been cut down, but was still above maintenance. The residual nitrogen fraction was at the upper borderline of the normal. The sugar tolerance was unchanged and was half the normal. Blood composition was normal. The patient had developed a secondary anæmia and a relative lymphocytosis. Skiagrams taken at this time showed a normal sella and sinuses and a suggestion of convolution impressions on the inner table. A pelvic examination disclosed no abnormalities. The eye examination showed a very slight enlargement of the blind spots.

*Discussion:* The second test was highly interesting and gave confirmation of the results of the first examination in an untreated patient. Again ovarian medication was strongly recommended at the time of the patient's discharge. We are advised that it has been followed (10 grains t. i. d.), and that while the patient has had a recurrence the duration of the psychotic period has been greatly lessened. Medication is being continued.

#### GROUP VIII. DEAFNESS

CASE S-813. The patient was a girl of 29, complaining of an increasing deafness in the left ear and a stationary loss in the right. As a child her hearing was normal. Impaired acuity was first noted at the age of 14, and then only in the right ear. At the age of 24

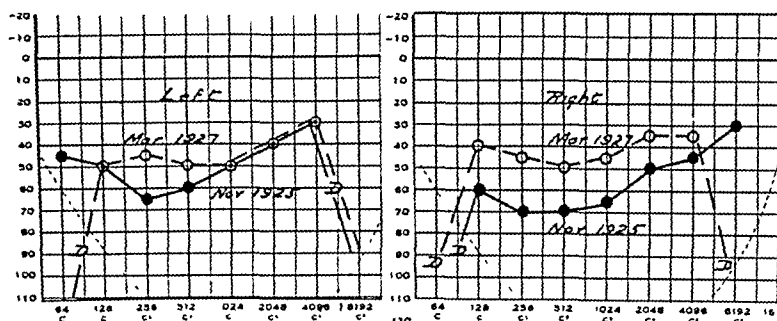


she found that the left ear had become involved, and this second condition had been progressive since that time. There was neither tinnitus nor paracusis.

*Family History* was not relevant.

*Past History:* The patient reported all of the minor ailments of childhood at an early age. She had influenza at the time of the epidemic, her age then being 22. In addition, she had had an appendectomy, with a later laparotomy for lysis of adhesions; two tonsillec-  
tomies and a dilatation and curettage operation for painful menstruation at about the time the second ear became involved. She complained of dull headaches, vertigo, susceptibility to colds, an abscess in the throat in 1910, and a fullness of the neck in the neighborhood of the thyroid. During the past three years she has become fatigable. She was markedly constipated and for a period of four years prior to her curettage she suffered from vomiting and pain in the right side. The menstrual history was normal and the remaining history not significant.

PLATE VI



Case S-813

*Physical Examination:* The patient was a well-developed, well-nourished girl, whose breath was slightly foul. There were tonsillar remnants and a slight thyroid enlargement; the abdomen was normal, as was the nervous system.

*Laboratory Summary:* The patient was 9 per cent above her predicted weight and showed a basal rate of —14 per cent, with low blood pressure. Alveolar carbon dioxide was normal. The urine was somewhat scanty, but was otherwise normal. Her protein intake was below a maintenance level, the residual nitrogen fraction high. The phthalein output was below normal. Her sugar tolerance was half the normal. The blood uric acid was relatively slightly high. The blood showed a somewhat low hæmoglobin and a slight leucocytosis, with substantially normal leucocytic formula.

*X-Ray Examination* showed some obscuration of all the sinuses.

*Barany Test* gave normal findings.

*Eye Examination* gave a positive Ewing test, with slight enlargement of the blind spots.

There was a definite loss of hearing in both ears, which were

*Discussion:* The presenting picture here was one of ovarian failure. Ovarian medication was recommended and for a time the patient followed it. The basal rate improved, also the blood pressure. There was no great change in the hearing, although some slight improvement was noted. More recently the patient has shown a return to the earlier level of hearing. She is seriously circumscribed and in anticipation of the future has begun to study lip reading. That she has not followed her medication there can be no doubt, although it is questionable if her patent endocrine defect and her hearing failure have any association. Correction of her pan-sinusitis was also recommended, but this, like her medication, has not been carried out.

**CASE S-1690.** There are several points of interest in this case, which is one of progressive deafness in a girl of 20. The condition began at the age of 10 and was progressive for a period of about 4 years. During the past 6 years it had remained unchanged so far as the patient could tell. There had been some catarrh during the early years, but this disappeared without any improvement in the hearing. The patient had been given pituitary extract at one time, but without affecting the deafness. The patient was a frail child, but with the establishment of the catamenia at the age of 12 she became more robust and was a healthy young girl at the time of her admission.

*Family History:* Cardio-renal disease and diabetes appeared several times among the immediate relatives.

*Past History:* She reported the minor ailments of childhood, a slight attack of tonsillitis, a partial tonsilectomy at 4 and a tonsil and adenoid operation at 12, and a brief attack of pyelitis at the age of 10. The patient reported a discharging ear early in the period of her deafness. This was, however, of brief duration. The remaining history, including that of the catamenia, was essentially irrelevant.

*Physical Examination* showed a well-developed and well-nourished girl. The speaking voice had the peculiar quality so frequently noticed in the deaf. There was excessive pilosity of arms, legs and spine, but the configuration of the pubic hair was normal. There was some acne on face and chin. The patient was distinctly deaf, but could apprehend loud speech. The blood pressure was low. The remaining findings were normal.

*Laboratory Summary:* The patient was within 1 per cent of her predicted weight. The basal rate was —12 per cent, blood pressure low, carbon dioxide a low normal. The urine and blood findings were normal, except for a slight lymphocytosis. The patient was in college and it was suggested that the tests of sugar tolerance be performed there. The whole general picture of the patient suggested an ovarian failure. Twenty grams of sugar were sent and the test was reported as negative. Later, a 40-gram test was also reported as negative. Sixty grams were sent, but as it was approaching vacation time the patient waited until she returned home to complete the test. In the meantime, examination of the existing data confirmed the earlier opinion of a probable gonad failure, with which the sugar test was wholly at odds. On the return of the patient to this neighborhood the sugar test was repeated with an initial dose of 20 grams, to which the patient gave a positive response. A second 40-gram dose gave a very marked positive response, while the response to 10 grams was negative.

*Nose and Throat Examination:* Tonsillar remnants were noted, but were apparently unoffending. There was a deflected septum, producing partial obstruction.

*Ear Examination* gave normal findings.

*Barany* test indicated normal conditions.

*Audiogram:* Marked uniform loss of hearing in both ears was disclosed.

*Radiography:* The sinuses were all normal. The patient showed one unerupted molar.

*Discussion:* The repeated sugar test completed the picture of a definite primary ovarian failure, and treatment with follicular hormone was recommended. It may well be argued that as the patient's deafness began before the establishment of the catamenia that there could be no connection between her presenting difficulty and her patent endocrine defect. We are wholly unwilling to attempt to establish any artefactual relationship between the two conditions. Recommendation for treatment of the endocrine condition was made solely to normalize the patient's general metabolism. That any betterment to the ear condition could accrue was wholly problematical. It should be said in passing that many of the subjects of deafness studied by us who demonstrate endocrine defects show a deafness which derives from a definite and demonstrably non-endocrine cause. The normalization of the endocrine status of such patients can only influence the hearing defect by indirection, if at all.

TABLE XXII

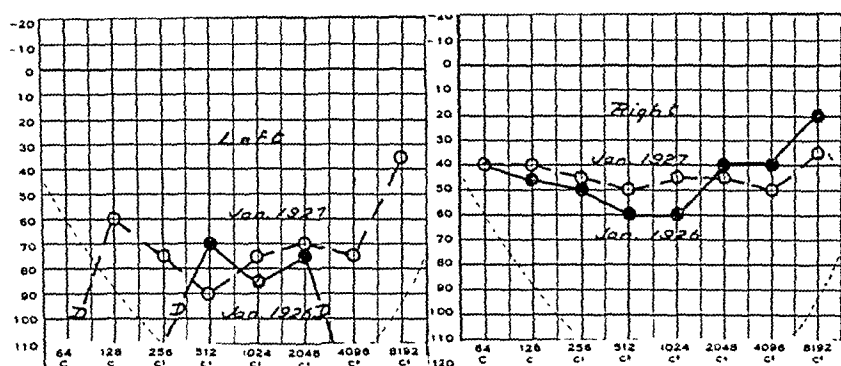
	Obesity					
	Genital Arrest		Castrate	Functional	Functional Failure	Azoospermia
Case Number.....	B-441	S-952	B-50	S-1229	B-610	S-1402
Sex.....	F	M	F	F	F	M
Age..... (yrs.)	21	10	51	39	15	27
Height..... (cm.)	148	116	154	159.0	142.7	180.5
Weight..... (kgm.)	48.6	5.5	110.0	94.5	39.5	84.5
Weight Deviation..... (%)	-2	+34	+107	+65	+7	+8
Lung Volume Deviation..... (%)	-33	-9	-58	-37	-15	+2
Basal Rate Deviation..... (%)	-17	-1	-17	-17	(+2*)	-3
Blood Pressure..... (mm.)	86/53	100/65	180/94	150/88	90/44	120/70
Pulse Rate..... (per min.)	76	86	56	67	72	72
Temperature..... (deg. F.)	97.2	99.6	97.0	97.8	98.2	97.2
Alveolar CO <sub>2</sub> ..... (mm.)	42	33	36	40	36	44
Urine Volume..... (cc.)	1180	1040	720	720	500	880
Spec. Grav.....	1.019	1.032	1.027	1.029	1.015	1.032
Albumin.....	+	0	0	0	+	0
Casts.....	+	0	0	0	0	0
Sugar.....	0	0	0	0	0	0
Total Nitrogen..... (gms.)	10.44	14.60	8.46	6.55	4.43	14.00
Residual Nitrogen..... (%)	15.1	6.6	11.3	6.6	4.9	11.0
Phen. Sulph. Phthal..... (%)	62	67	42	52	53	49
Galac. Tol.—						
Normal..... (gms.)	40	30	20	40	40	
Observed..... (gms.)	20	30	20	30	20	not done
Deviation..... (%)	-50	±0	±0	-33	-50	
Blood—						
Non-Protein Nitrogen..... (mgm.)	27	33	33	27	37	29
Uric Acid..... (mgm.)	3.0	2.9	5.3	3.0	3.7	3.7
Sugar..... (mgm.)	91	(118)	(113)	107	93	90
Haemoglobin..... (%)	100	85	100	70	80	90
Erythrocytes..... (10 <sup>6</sup> )	5.30	5.56	5.12	3.80	4.80	4.50
Leucocytes..... (10 <sup>3</sup> )	10.20	13.20	7.70	9.80	6.50	9.40
Neutrophils..... (%)	69	75	32	69	44	71
Lymphocytes..... (%)	24	20	54	27	44	20
Eosinophiles..... (%)	1	0	10	1	3	3
Monocytes..... (%)	6	5	2	3	9	6
Misc..... (%)	0	0	2	0	0	0

## GROUP IX. DEVELOPMENT ARREST

**CASE B-441.** The patient was a 21-year-old girl whose chief complaint was of physical and mental retardation. She was also very deaf in the left ear, less so in the right. The patient was an eight-months baby, and at birth was not expected to live. She showed developmental retardation from birth, being 4 years old before she began to talk. The developmental retardation has been even more marked since her fourteenth year, at which time the period first appeared. Her deafness also dated back to early childhood. There was no paracusis, some tinnitus and no apparent change in her deafness for some years past. The various deficiencies had brought about a shut-in existence, though the patient was not outspokenly asocial.

**Family History:** Twin sisters of the patient died a few hours after birth. There were several other surviving children, all of whom were normal.

## PLATE VII



Case B-441

**Past History:** The patient reported minor ailments and a tonsil and adenoid operation at 17. The remaining history, including that of the catamenia, is entirely uneventful.

**Physical Examination:** The patient was of small stature and fairly well proportioned, although the chest and hips were relatively somewhat large. There was a marked hair growth on the arms and legs and the heavy pubic hair showed a masculine type of distribution. There was obviously marked mental retardation. Much acne was observed on both face and back. Both ears were deaf, the right less markedly so. Some tonsillar remnants were noted. There was a loud systolic murmur at the cardiac apex transmitted to the axilla, a systolic murmur over the base transmitted to the neck and more pronounced over the aortic area.

**Laboratory Summary:** The patient was less than 5 feet tall; her sitting height index was high, so that she was actually overweight instead of the 2 per cent below prediction which was recorded. The basal rate was —17 per cent, with low blood pressure. Both albumin and casts were reported in the urine and the residual nitrogen was very high. The sugar tolerance was half the normal level.

**Radiography:** The skull was normal.

**Audiogram:** The patient showed a marked loss of hearing in the right ear, and positive hearing in the left was obtainable only at frequencies of 512, 1024, and 2048 (see plate).

*Neurological Examination* disclosed gross change in the 8th nerve and various vegetative disturbances.

*Ear Examination:* The drums were retracted and the cones of light were broken.

*Pelvic findings* were normal, except for the excessive hirsuties.

*Eye findings* were apparently normal.

*Discussion:* The patient presented a picture strongly suggesting ovarian failure. Attention is called in this connection to the high sitting height index, a condition on which comment has already been made. She was placed on ovarian medication (follicular hormone), and one year later was returned to the Clinic for brief study. The height was unchanged, but she had increased 4 kgm. in weight. The basal rate was —9 per cent and the blood pressure 110/60. The lowered sugar tolerance had become normal, 40 grams being necessary to produce a positive response. The audiogram showed a striking improvement (see plate). There was also said to be definite evidence of clinical betterment.

CASE S-952. The patient was a boy of 10 who was referred for obesity, genital arrest, and feminine contour of body. Prior to the time of birth the mother became very toxic and delivery was advised in the seventh month. She carried him to term, however, and was delivered by a high forceps operation. He weighed 9½ pounds at birth, but the genitalia were very small. He did not talk until he was 3 years old. At 4 he had a severe case of whooping cough, followed by bronchial pneumonia. Since then he had had frequent recurrent attacks of bronchitis. The obesity developed after the pneumonia. He had always shown a preference for female companions and was constantly seeking to be kissed by his female relatives, but within the last few months he had begun to play only with boys and had lost his desire to be fondled. He had made an unusually good record in school and had shown unusual musical gifts.

*Family History* was irrelevant.

*Past History:* Only minor ailments of childhood in addition to the record given above were reported. A tonsil and adenoid operation was performed 3 years ago. He had an occasional severe headache. Some years previously "a gland in the middle of the neck became inflamed, but subsided spontaneously." He was constipated when very young.

*Physical Examination:* The boy was an obese lad of 10, with very wide hips, very small genitalia, and large breasts of the feminine type. There was a large pad of fat below the umbilicus. The very small testicles while being examined were retracted into the ring. The boy showed third degree flat-foot and no pilosity.

*Laboratory Summary:* The boy was reported as 34 per cent overweight, with a fairly normal sitting height index. The basal rate was 1 per cent below prediction, blood pressure low, and the pulse somewhat rapid. There was a slightly febrile temperature, and if correction were made for this it would reduce the basal rate deviation to about the low normal level. The sugar tolerance was normal; in fact, all of the other observations were normal, with the exception of a slight leucocytosis.

*Radiography:* The skull was normal.

*Eye Examination:* Normal.

*Discussion:* The picture presented here was similar in kind to that produced by castration. The boy was reported by us as a con-

genital gonad failure. As there was no reason to anticipate betterment from any of the suggesting methods of treatment, no recommendations as to therapy were made. The boy was requested to return in 2 years for a repetition of the study.

#### GROUP X. OBESITY

**CASE B-50.** The patient was an extremely obese woman 51 years of age who had had a pan-hysterectomy 28 years before. She was married 30 years earlier, and in the brief interval of 2 years conceived twice, but each time induced abortion in the second month. A hysterectomy was then performed, although the patient did not know the reason for this operation. She weighed 135 pounds at the time of her marriage. After her operation she began to increase in weight and a year before she was admitted to this Clinic weighed over 260 pounds. She stated that diet was ineffective in weight reduction, but that for 15 years past she had been taking thyroid intermittently, at times reaching 8 grains a day. She stated that under thyroid medication she always lost weight, but became very weak and suffered from palpitation. She had been without medication for some time prior to her admission. She also complained of a throat trouble which began 15 years before and consisted chiefly of a dry, scratchy sensation.

*Family History:* One sister had diabetes. The remaining history was irrelevant.

*Past History:* In addition to the matters detailed above, the patient reported minor ailments, diphtheria, typhoid, influenza, and frequent attacks of pharyngitis. She had had some loss of hearing in the left ear for many years. The teeth were in fair condition. She complained of attacks of hoarseness. The gastro-intestinal history was entirely normal. She denied venereal disease, and we were unable to secure the information on this point that we desired. The Wasserman reaction was negative. She complained of some nocturia. The menses were established at the age of 12 and the history was uneventful up to the time of her operation. She had used alcohol freely throughout her life.

*Physical Examination:* The patient was a very obese woman of 51, the trunk being relatively more obese than the legs. The pupils were sluggish in their reaction to light, but reacted well to accommodation and were equal and regular. The tongue showed no tremor, the teeth were in poor condition, there was no thyroid enlargement, the breasts were very large and pendulous. Coarse, bubbling rales were noted, most marked at the end of expiration and confined to the right side. They were increased by coughing. The blood pressure was very low. The abdomen was normal. The routine neurological findings were normal.

*Laboratory Summary:* The patient was just over 5 feet tall and 107 per cent above her predicted weight. Her sitting height index was substantially normal. There was marked loss in lung volume. The basal rate was —17 per cent, with a somewhat slow pulse and a hypertensive blood pressure. Alveolar carbon dioxide was low. The urine was somewhat scanty, otherwise not remarkable. Residual nitrogen was high; the phthalein output below the normal. The patient gave a positive test with 20 grams of galactose, the level to be predicted from the history of her earlier operation, and negative with 10. There was a high blood uric acid, a marked lymphocytosis, and a 10 per cent eosinophilia.

*Ear Examination:* The drum heads showed a moderate degree of chronic catarrhal thickening. In addition, the examiner found evidence of a low degree of toxæmia affecting the auditory nerve.

*Nose and Throat Examination:* There was a slight septum deviation, somewhat large, cryptic tonsils, and a slight inflammatory condition of the larynx.

*Radiography:* The skull and chest were normal, though the plates of the latter were somewhat unsatisfactory because of the thick chest wall.

*Discussion:* The whole history of this case, coupled with the laboratory examination, suggests an obesity arising from the patient's surgical hypogonadism. There is no suggestion here of thyroid failure which could not equally be referable to the ovarian loss. The œsinophilia and high blood uric acid would carry a suggestion of pituitary involvement, which was, however, denied by certain of the other observations. We were not able to complete the study on this patient and the chest condition, and that of the cardio-vascular system remained largely unevaluated. The patient was recommended to take ovarian medication, but the habit of years determined her to continue with the thyroid. We speedily lost track of her, but one of us learned later that she had become psychotic and had died within a few years of the study at the Boston Psychopathic Hospital. As noted above, complete cooperation could not be secured and the study, of necessity, remained incomplete.

CASE S-1229. This patient was a very obese woman, 39 years of age, who complained of cramp in the upper abdomen. The onset of this condition had been a few days before. She also complained of her obesity, which apparently began in young girlhood. For a number of years she had been increasingly fatigable, and with the onset of the pain element had become nervous and irritable. There was reason to believe that this latter factor was of materially longer duration than the preceding few days.

*Family History:* There were numerous records of cardio-renal and cardio-vascular disease in her immediate family.

*Past History:* She reported the minor ailments of childhood, a tendency to infections of the respiratory tract, and rheumatism. She had had tonsilitis and endocarditis in 1917. She had worn glasses for the last 5 years, and when tired was unable to focus the eyes properly. She had had several attacks of conjunctivitis in the left eye within the past few months. She was troubled with flatulency, but only when nervous and tired. The catamenia was established at the age of 11; the periods were regular at 42-day intervals, the flow was scanty.

*Physical Examination:* The patient was a very obese woman with the fat generally distributed, presenting hypertrichosis on the face, heavy hair growth on the arms and legs, and masculine distribution of heavy pubic hair. The palms of the hands showed a slight eczematous involvement. The majority of the teeth were missing, and those remaining were in only fair condition. The tonsils were hypertrophied and apparently not offending. There was a slight systolic murmur and a slightly high blood pressure. The remaining findings were not remarkable.

*Laboratory Summary:* The patient was 65 per cent above her predicted weight, with normal sitting height index. She was definitely below her predicted lung volume. The basal rate was —17 per cent, the blood pressure somewhat high. The urine was scanty and

concentrated, but otherwise normal. The sugar tolerance was somewhat depressed; blood composition normal, but with some degree of secondary anæmia.

*Eye Examination:* The left upper form field was somewhat cut, due to a drooping eyelid; the remaining findings were normal.

*Discussion:* Only a limited study could be made on this patient and emphasis was laid on the purely endocrine aspects. The picture presented was suggestive of primary ovarian failure, although a pituitary dysfunction was not excluded. Ovarian medication was recommended and we believe has been followed in some measure. Indirect report suggests some but not striking improvement.

#### GROUP XI. FUNCTIONAL FAILURE IN EARLY ADOLESCENCE

CASE B-610. This patient was a 15-year-old girl whose presenting difficulty was her small stature, she being but 4 ft. 9 in. tall. From the time of her early childhood she had been smaller than the other girls of her own age.

*Family History* was entirely irrelevant. Three siblings died in infancy of diphtheria, and five surviving brothers and sisters were all normal.

*Past History:* The patient had influenza at the age of 7 and pneumonia a year later. The catamenia was established eight months before, and in this interval the patient had had four periods which were substantially normal. The remaining history was not significant.

*Physical Examination:* The patient was a small, well-developed and well-nourished girl of 15. There was a very slight thyroid enlargement, a few moist rales at the right apex, increased vocal fremitus in the interscapular region; the knee jerks were sluggish. The remaining findings were completely normal.

*Laboratory Summary:* The patient was 7 per cent above her predicted weight, with normal sitting height index. The basal rate as recorded was 2 per cent above prediction. This was incorrect and the test was not entirely satisfactory; the true rate was undoubtedly below this level. A second examination could not be secured. The blood pressure was definitely low, as was the carbon dioxide. The urine was scanty and contained albumin. The protein intake, as indicated by the nitrogen elimination, was below a maintenance level. The residual nitrogen fraction was normal. The sugar tolerance was half the normal level. The nitrogenous elements of the blood were slightly high. The blood showed a relative lymphocytosis and a 3 per cent eosinophilia.

*Radiography:* The bone development of the knees and shoulders was normal; the sella shows enlarged posterior clinoids.

*Discussion:* This case again could be regarded as one of pituitary dysfunction. The bulk of the evidence, however, was more suggestive of an inadequacy of gonad function. She is reported as improved, but we have had no further contact with her.

CASE S-1402. The following case is particularly interesting in view of certain beliefs that have been generally current during the past few years in relation to bodily vigor, libido and the status of the male gonads.

The patient was a large, powerful man of 27, whose complaint



was of sterility. He had been married for about two years and had had satisfactory intercourse every night since his marriage, with the exception of two or three intervals of 3-4 days each. He had no difficulty in securing an erection, but believed that his ejaculation time was somewhat rapid, as he would have his orgasm within twelve or fifteen strokes after immission. His deduction is not necessarily correct, as both he and his wife always have orgasm. In 1917, ten years previously, he had had the mumps with orchitis as a complication. Several examinations since marriage had shown a complete absence of spermatozoa from the semen.

*Family History* showed one case of cancer, but was otherwise irrelevant.

*Past History:* In addition to the mumps he reported the minor ailments of childhood, scarlet fever, influenza at the time of the epidemic, and recurrent sore-throats in childhood, with one quinsy. He had headaches as a boy; none for several years, however. The remaining history was entirely normal. The patient was the driver of a truck, handling groceries in bulk, such as barrels of sugar and large cases of canned goods. He worked from 3 a. m. to noon, and acknowledged that "at times he felt tired at the end of the day's work." Three years previously he had strained his side in lifting a barrel of sugar, but examination showed it to be no more than this, and he had had but little subsequent trouble from it.

*Physical Examination* showed a very well developed, muscular young man. The nose showed some obstruction and the presence of a serous discharge (the patient had a head cold); the teeth were in fair condition only; the tonsils were somewhat hypertrophied. A few moist rales were noted at the right apex. Body hair was normal in amount and distribution. The testicles were less than half the normal size and there was a small left varicocele. The remaining findings were normal.

*Laboratory Summary:* The patient was nearly six feet tall; he was 8 per cent overweight and slightly above his predicted lung volume. The basal rate was entirely normal, as were the complementary measurements. Only the temperature was slightly low. The urine had a slightly low volume, but elimination was fair. The residual nitrogen fraction was high; the remaining findings normal. The blood cells showed a predominance of neutrophils and a 3 per cent eosinophilia. The blood uric acid was relatively high, the serological findings were normal.

*Laryngological Examination:* The tonsils were found to be definitely infected.

*Cystoscopy* showed a small degree of posterior urethritis.

*Eye Examination:* The blind spots were slightly enlarged.

*Genito-urinary Examination:* The two lobes of the prostate were slightly enlarged and boggy. Several condom specimens showed complete azoospermia.

*Neurological findings* were normal.

*Discussion:* We regard this case as peculiarly informative. The patient is a young man with markedly atrophied testes and seemingly a complete loss of spermatogenic function. Physically he is vigorous, hardy and strong beyond the average. Sexually, his libido and his power to have intercourse, satisfactory to himself and his partner, is distinctly above the average. Diagnoses of hypergenitalism

have been made on a less enduring performance than is his, and yet there is a demonstrable gonad failure so far as the exocrine function is concerned. We do not attempt to explain it. We only offer the facts.

Review of the preceding protocols demonstrates one striking difference between the cases presented and those recorded in the earlier thyroid and pituitary papers. A number of them derived from a mutilating operation with complete removal of the endocrine organs. For these, naturally, no effective treatment was available. Some of the others resulting from functional failure were placed under endocrine medication and responded favorably. In many instances, however, recourse to endocrine therapy was seemingly ineffective. This outcome must be regarded as the result of several factors. In the first place, review of the individual case protocols will disclose a record of many incomplete studies, left so because of the incooperation of the patient. Comment has been made in the body of the paper on the personality change frequently associated with ovarian failure. This has operated not only to lessen the thoroughness of the particular individual studies but also has hindered a faithful performance of the therapeutic program suggested. A second factor is found in the inadequacy of the medication. Many ovarian preparations apparently are relatively inert and the huge dosage which would be necessary to secure adequate response is but seldom offered. As already noted in the pituitary paper, one prime factor in the frequent statement that anterior lobe medication is ineffective rests upon the failure of the physician in charge of the case to prescribe an adequate dosage. As recorded in the earlier paper, one of the patients in the pituitary series showed definite improvement only with a level of medication of 104 grains of anterior lobe material daily. Many others seemingly required a daily intake of from 50 to 75 grains to restore them to a normal functional level. Thanks to the brilliant work of several investigators, among whom Doisy and Allen (57) should not fail of mention, more active ovarian material is now available for clinical use. Results obtained with this are far more encouraging and productive in our experience than was usually the case with the earlier preparations. The subject is a large one and equally one of great importance. It is planned by one of us (C. H. L.) to present in the near future a much more extended analysis of the results

of ovarian therapy than could suitably find place in this article. It is permissible, however, to say that in the more recent cases in which ovarian therapy has been indicated by the establishment of a diagnosis of primary ovarian failure, the results are far more encouraging and hopeful than was formerly the case. While these materials have not been available for a sufficiently long time to allow for such thorough studies of the results of medication as are available for the pituitary and the thyroid investigations, the trends of betterment disclosed warrant the same degree of confidence in the validity of diagnoses as are given by the results of therapeutic testing in pituitary and thyroid disorders.

The cases in the foregoing section were selected to illustrate some given point as strikingly as possible. Many of the other cases in the series presented uncomplicated functional failures, and a large part of these have responded satisfactorily to treatment. As cases, they are lacking, however, in the distinctive special features of those selected for this series of protocols and their consideration belongs more properly to the forthcoming paper which will be devoted primarily to a discussion of the results of treatment.

The authors wish to express their sincere and grateful thanks to the colleagues and associates who as members of the staff have contributed so much to their studies, to their other colleagues from whose reference have derived many of the interesting and significant cases in the series and finally to the patients themselves for their cooperation in the work.

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# STUDIES OF OXYTOCIN AND VASOPRESSIN: THE EFFECT ON FROG MELANOPHORES

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DETROIT

The effect of pituitary posterior lobe extracts upon the pigment system of Amphibia has been the subject of careful investigation by groups of English workers, particularly Hogben and Winton (1 and 2). These authors reported upon the specificity of potent pituitary extracts as melanophore stimulants, using frogs (*Rana temporaria*) as test animals. The earlier work of Spaeth (3) on fish, and Swingle (4) and McCord (5) on tadpoles, was also considered. They decided that the melanophore stimulant is probably identical with the oxytocic principle, and that this test could be used as a quantitative means of assay for pituitary extracts (2).

Other workers—Dreyer and Clark (6), Schlapp (7), and Fenn (8)—reported later that the melanophore stimulant and the pressor principle are probably identical, thus opposing the views held by Hogben and Winton. Since the definite separation of two active principles from pituitary extracts by Kamm, Aldrich, Grote, Rowe and Bugbee (9), it seemed desirable to subject these separated principles to tests on frog melanophores to determine whether this action could be ascribed to either or to both of them.\* The value of this melanophore stimulant method as a quantitative means of assay for one or the other of these principles, and the mechanism of the action on the melanophores, seemed also worthy of investigation.

Accordingly, experiments were begun, using frogs (*R. pipiens*) as the test animals, without decerebration but after "bleaching" in bright light on a white background. Injections were all 0.5 cc. in volume, and made intraperitoneally into medium sized frogs, room temperature (about 25° C.) being used. A series usually consisted of 4 frogs of about the same weight,

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\* Communication to Dr. Kamm, Prof. C. G. MacArthur, of the reports that the pressor principle is responsible for melano-

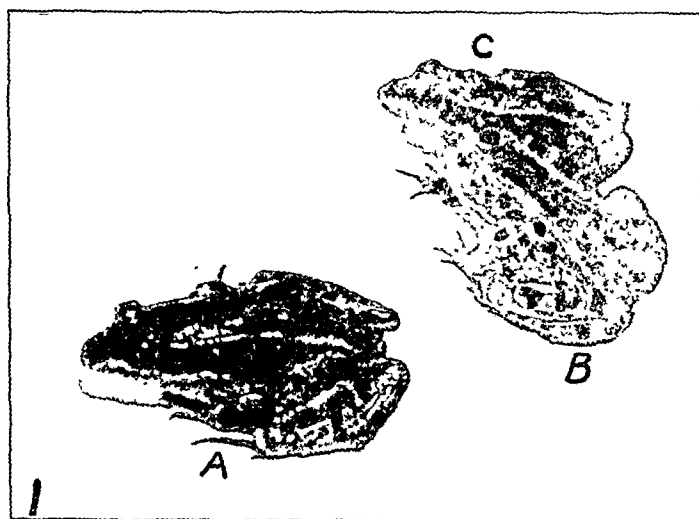
one of which received a dilution of the oxytocic principle (Oxytocin) equivalent to standard U. S. P. X pituitary extract; another a dilution of the pressor principle (Vasopressin), equivalent to standard surgical Pituitrin in pressor potency; another, a dilution of standard surgical pituitary extract (Pituitrin, S), and the fourth served as a control. The control frog was frequently not injected at all, but sometimes was injected with salt solution and sometimes with distilled water. Some twenty series were injected and the results in each series may be briefly detailed as follows:

Series	Frog Wt.	Dose	Melanophore Effect
1	10 gms.	Vasopressin, 1-2000	Expanded. Visibly dark +++
1	12 gms.	Oxytocin, 1-1000	Very slightly visible, +
1	10 gms.	Pituitrin "S," 1-2000	Very slightly visible, +
2	13 gms.	Oxytocin, 1-1000	No visible effect, 0
2	12 gms.	Pituitrin "S," 1-2000	Slightly visible, ++
2	12 gms.	Vasopressin, 1-2000	Very slightly visible, +
3	14 gms.	Pituitrin "S," 1-1000	Very dark $\frac{1}{4}$ to 1 $\frac{1}{2}$ hrs., ++++
3	13 gms.	Oxytocin, 1-500	No visible effect, 0
3	13 gms.	Vasopressin, 1-1000	Dark $\frac{1}{4}$ to 1 $\frac{1}{2}$ hrs., +++
3	12 gms.	Ringers Sol.	No visible effect, 0
4	13 gms.	Pituitrin "S," 1-1000	Very dark in $\frac{1}{2}$ hr., +++
4	14 gms.	Vasopressin, 1-1000	Quite dark in $\frac{1}{2}$ hr., +++
4	17 gms.	Oxytocin, 1-200	No visible effect, 0
5	14 gms.	Oxytocin, 1-200	No visible effect, 0
5	14 gms.	Vasopressin, 1-1500	Very slight, +
5	18 gms.	Pituitrin "S," 1-1500	Dark when dosed, became darker
6	12 gms.	Pituitrin "S," 1-1000	Very dark, ++++
6	14 gms.	Oxytocin, 1-50	Very slight +. Prostrated in 2 hrs.
6	16 gms.	Vasopressin, 1-1000	Dark, +++
7	15 gms.	Oxytocin, 1-100	No visible effect, 0
7	16 gms.	Pituitrin "S," 1-1500	Very dark $\frac{1}{4}$ to 1 hr., ++++
7	15 gms.	Vasopressin, 1-1500	Dark $\frac{1}{4}$ to 1 hr., +++
8	14 gms.	Oxytocin, 1-100	No visible effect, 0
8	15 gms.	Vasopressin, 1-2000	Fairly dark, ++
8	15 gms.	Pituitrin "S," 1-2000	Dark, +++
8	14 gms.	Distilled water	No visible effect, 0
9	16 gms.	Vasopressin, 1-1000	Dark $\frac{1}{4}$ hr. to 1 hr., +++
9	17 gms.	Pituitrin "S," 1-1000	Very dark $\frac{1}{4}$ to 1 hr., ++++
9	18 gms.	Oxytocin, 1-100	Light, 0
10	18 gms.	Oxytocin, 1-100	Light, 0
10	16 gms.	Pituitrin "S," 1-1500	Very dark $\frac{1}{2}$ to 1 $\frac{1}{2}$ hrs., ++++
10	19 gms.	Vasopressin, 1-1500	Dark $\frac{1}{2}$ to 1 $\frac{1}{2}$ hrs., +++
11	20 gms.	Oxytocin, 1-100	Light, 0
11	18 gms.	Vasopressin, 1-1000	Dark, +++
11	18 gms.	Pituitrin "S," 1-1000	Very dark, ++++
12	12 gms.	Pituitrin "S," 1-2000	Dark in $\frac{1}{2}$ hr., +++
12	12 gms.	Oxytocin, 1-100	Dark in $\frac{1}{2}$ hr., +++
12	12 gms.	Vasopressin, 1-2000	Dark in $\frac{1}{2}$ hr., +++
13	20 gms.	Pituitrin "S," 1-1000	Very dark in $\frac{1}{4}$ to 1 hr., ++++
13	20 gms.	Oxytocin, 1-50	Light all the time, 0
13	20 gms.	Vasopressin, 1-1000	Dark in $\frac{1}{2}$ hr. to 1 hr., +++
14	19 gms.	Oxytocin, 1-100	Slightly dark, +
14	20 gms.	Pituitrin "S," 1-1000	Fairly dark, ++
14	18 gms.	Vasopressin, 1-1000	Fairly dark, ++
15	14 gms.	Vasopressin, 1-2000	Dark in $\frac{1}{4}$ to 1 hr., +++
15	14 gms.	Oxytocin, 1-100	Light all the time, 0
15	14 gms.	Pituitrin "S," 1-2000	Very dark, ++++
16	15 gms.	Vasopressin, 1-2000	Medium to light, ++
16	16 gms.	Oxytocin, 1-100	Light all the time, 0
16	14 gms.	Pituitrin "S," 1-2000	Dark, +++
17	18 gms.	Vasopressin, 1-3000	Dark in $\frac{1}{4}$ to 1 hr., +++
17	18 gms.	Oxytocin, 1-100	Light all the time, 0
17	18 gms.	Pituitrin "S," 1-3000	Very dark $\frac{1}{4}$ to 1 hr., ++++
18	17 gms.	Vasopressin, 1-4000	Dark $\frac{1}{2}$ to 1 hr., +++
18	16 gms.	Oxytocin, 1-100	Lighter than when dosed, 0
18	18 gms.	Pituitrin "S," 1-4000	Dark $\frac{1}{2}$ to 1 hr., ++++

Series	Frog Wt.	Dose	Melanophore Effect
19	12 gms.	Vasopressin, 1-4000	Fair, ++
19	12 gms.	Pituitrin "S," 1-4000	Dark, +++
19	16 gms.	Oxytocin, 1-500	Light all the time, 0
19	20 gms.	Pituitrin "S," 1-5000	Fair, ++
		20th Series. Carefully decerebrated	
	15 gms.	Pituitrin "S," 1-4000	Very dark, ++++
	12 gms.	Vasopressin, 1-4000	Dark, +++
	12 gms.	Oxytocin, 1-100	Light, 0
		21st Series. Carefully decerebrated	
	10 gms.	Vasopressin, 1-5000	Fair, ++
	10 gms.	Pituitrin "S," 1-6000	Dark, +++
	10 gms.	Oxytocin, 1-50	Very dark (later lighter), ++++
	15 gms.	Distilled water	Slight, +
		22nd Series. Carefully decerebrated	
	15 gms.	Vasopressin, 1-8000	Fair, ++
	15 gms.	Pituitrin "S," 1-10,000	Fair, ++
	15 gms.	Oxytocin, 1-80	Fair, ++
	15 gms.	Control, not dosed	Slight, +
		Isolated Skin Tests	
	Strip of web	Vasopressin, 1-4000	Fair, ++
	Strip of web	Oxytocin, 1-100	Slight, +?
	Strip of web	Pituitrin "S," 1-4000	Contracted ?
	Strip of web	Vasopressin, 1-1000	Good, ++++
	Strip of web	Oxytocin, 1-50	Some, +
	Strip of web	Pituitrin "S," 1-1000	Good, ++++

# DISCUSSION

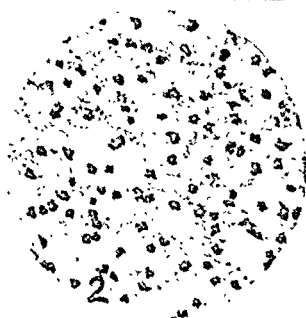
In considering roughly the results detailed above, it can be seen that melanophores of the intact frog (*R. pipiens*) are quite sensitive to pituitary extract (Pituitrin) and to its pressor principle (Vasopressin). The melanophores are not appreciably ex-



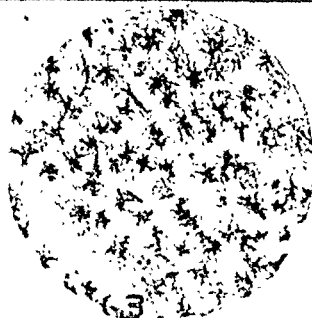
A=PITUITRIN "S," 1/3000. B=OXYTOCIN, 1/100. C=VASOPRESSIN, 1/3000.

panded by relatively large doses of the oxytocic principle (Oxytocin). These facts are apparent from macroscopic observation of the intact animals, and the photograph (No. 1) illustrates this.

Most of the experiments were made with intact animals, rather than by following the technique of Hogben and Winton (1) because it seemed desirable to simplify the test, if possible, in order to put it on a practical basis; and also it was quickly



*Oxytocin 1/100 Intact Frog*



*Vasopressin 1/3000 Intact Frog*



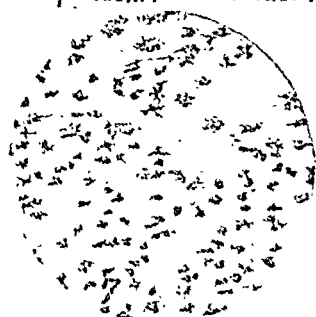
*Pituitrin S 1/3000 Intact Frog*



*Vasopressin 1/4000 Intact Frog*



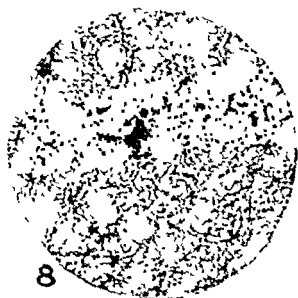
*Pituitrin S 1/4000 Intact Frog*



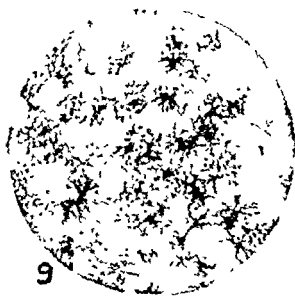
*Pituitrin S 1/5000 Intact Frog*

observed that the intact animals were very sensitive, though not as sensitive as the decerebrated animals. The results with the intact animals were sufficiently erratic to indicate that it would not be a suitable method for quantitative control of pressor





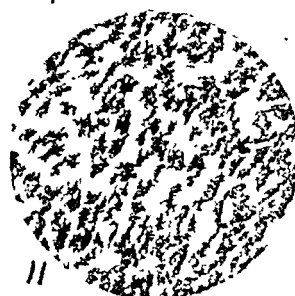
8  
*Pituitrin S 1/4000 Intact Frog*



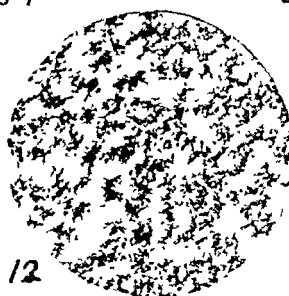
9  
*Vasopressin 1/4000 Intact Frog*



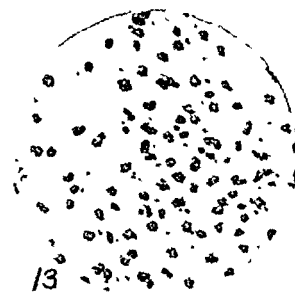
10  
*Oxy. 1/100 Decerebrate Frog*



11  
*Vaso. 1/2000 Decerebrate Frog*



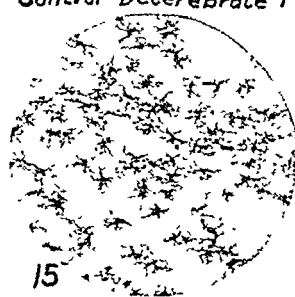
12  
*Pit. S 1/2000 Decerebrate Frog*



13  
*Control Decerebrate Frog*



14  
*Vaso. 1/1000 Isolated Web*



15  
*Pit. S Isolated Web*

activity, even if the pressor and melanophore principles are actually identical. This is contrary to the quantitative accuracy reported by Hogben and Winton (2) and confirmed by Treuter (10). Kochmann and Wagner (11), however, find the method not more than roughly quantitative.

The tests on the decerebrated animals show them to be more sensitive and probably more accurate, but the quantitative pressor test of Hamilton (12) is much more logical and fully as accurate as a means of assay for the pressor principle.

Grossly, it can also be seen from results on the intact and decerebrated animals that the pressor principle alone (Vasopressin) is appreciably less powerful as a melanophore stimulant than is a pituitary extract of the same pressor potency (Pituitrin, S). The difference in favor of the pituitary extract seems to be about 20 to 25 per cent. This fact is very difficult to explain, if we assume that there are only two active principles in the activity of the posterior lobe. About the only explanation would be the possible divergence due to the sum of the known experimental errors of the pressor and melanophore methods. In that case, there would actually be the difference in *pressor activity* between the Vasopressin and Pituitrin which is apparent by the melanophore tests. This explanation is made rather untenable, however, by the fact that in my experiments several different lots of Vasopressin and Pituitrin S were used, and the pressor experimental error could not always have diverged. The more logical explanation seems to lie in the possibility of a third active principle which is more closely associated with the pressor principle, and consequently has only been partially separated from it in our Vasopressin. This, of course, is only a theory which has not been proved or disproved at this time.

As visible proof of the powerful effect of dilute solutions of Pituitrin and Vasopressin, and the lack of effect of Oxytocin upon the melanophores, the following photomicrographs are presented. A piece of the web of the foot was removed, usually 30 minutes after injection, when the effect was at its height, fixed in formalin and mounted on a microscopic slide. This proved much more satisfactory than fixing skin from the back in Bouin's fluid, as was done by Hogben. These photomicrographs speak for themselves in showing the lack of melanophore stimulant

activity of Oxytocin in 1-100 dilution, but some action in 1 to 50 dilution. They also show the appreciable difference between Vasopressin and Pituitrin, S, though these products have approximately the same pressor activity.

The question of the mode of action of pituitary extracts upon the melanophores has been carefully considered by Hogben and Winton (1). They showed that since pituitary extract acts upon melanophores of isolated frog skin, and since it acts upon melanophores after paralysis of the nerve endings, the action must be a direct one upon the pigment cell itself. This mode of action of Vasopressin has been confirmed to the extent that it acts upon isolated strips of web from the foot of the frog, as shown by the few experiments conducted and the photomicrographs of stimulant action from 1-1000 Vasopressin and Pituitrin, but little action even from a 1-50 dilution of Oxytocin. It would certainly seem that the stimulant action is a specific and direct one upon the cell itself.

#### CONCLUSIONS

1. Oxytocin, a solution of the oxytocic principle equivalent to U. S. P. X standard pituitary extract in uterine stimulating activity, does not stimulate frog melanophores.

2. Vasopressin, a solution of the pressor principle, does stimulate frog melanophores, but apparently to an appreciable degree less than a pituitary extract of the same pressor potency.

3. The melanophore stimulant present in pituitary extract may be a separate principle which is more closely associated with the pressor than with the oxytocic principle.

4. The melanophore method is erratic and less sensitive when intact frogs are used, and would not be a suitable bioassay control method for the *pressor* activity of pituitary extract.

5. The mode of action of the melanophore stimulant is apparently a direct one upon the cell itself.

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2. Hogben and Winton: Studies on the pituitary. I. The melanophore stimulant in posterior lobe extracts. *Biochem. J.* **16**: 619. 1922.
3. Spaeth, R. A.: Concerning a new method for the biological standardization of pituitary extract and other drugs. *J. Pharm. & Exper. Therap.* **11**: 209. 1917.

precipitants used are the organic solvents, acetone, sulphuric ether, and petroleum ether, none of which injure the physiologically active substances.

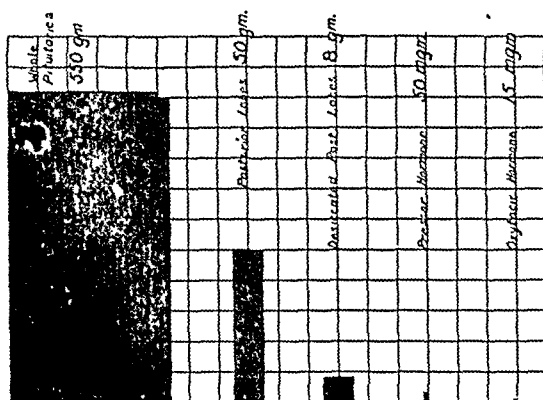
The two hormones, although so very unlike in their physiological behavior, resemble each other not only in chemical nature but also in many of their physical properties, and it is therefore not surprising that as many as twenty fractionations must be conducted in order to secure a satisfactory separation. This is illustrated by the results shown in Table I.

TABLE I

Separation of Oxytocic from Pressor Fraction

	Ratio of Pressor to Oxytocic Activity
Second Fractionation .....	100 : 60
Third Fractionation .....	100 : 24
Fourth Fractionation .....	100 : 14
Fifth Fractionation .....	100 : 12
Sixth Fractionation .....	100 : 10
Seventh Fractionation .....	100 : 8.5

Following such an exhaustive fractionation the separate fractions may be recombined, dissolved in acidified water, and diluted back to the original volume, yielding a solution that is



Pituitary Glands from 200 Steers

FIGURE 1

indistinguishable from the original gland extract, thus showing that in the process none of the activity has been injured or one product converted into another.

Figure I shows graphically the relative amounts of pituitary glands and active principles obtained.

Two hundred beef pituitaries weigh 550 grams. The posterior lobes alone weight 50 grams. When desiccated, the posterior lobes weigh only 8 grams. The purified pressor fraction weighs only 0.050 gram and the oxytocic fraction weighs only 0.015 gram. Work is in progress aiming to obtain them in a condition of absolute purity.

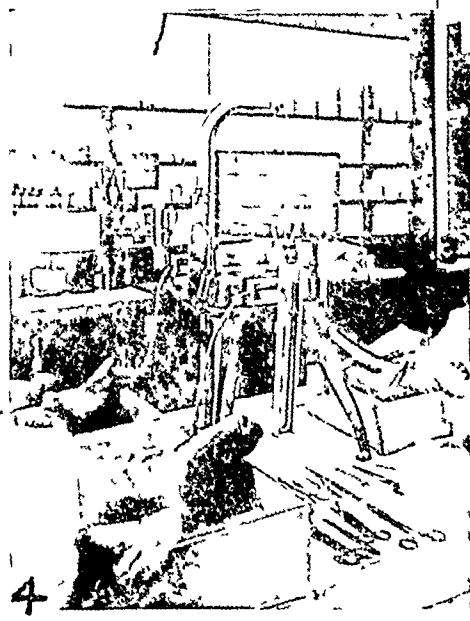
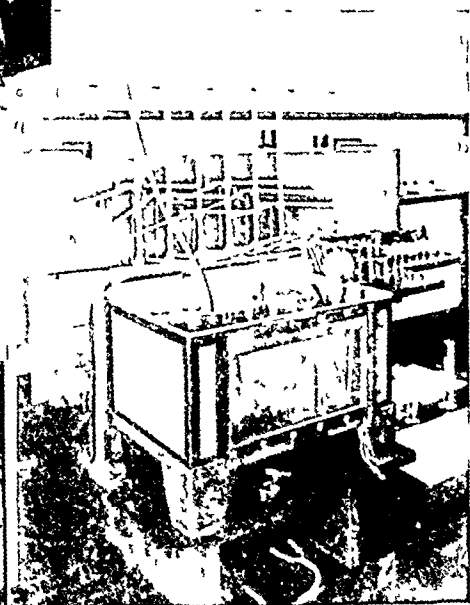
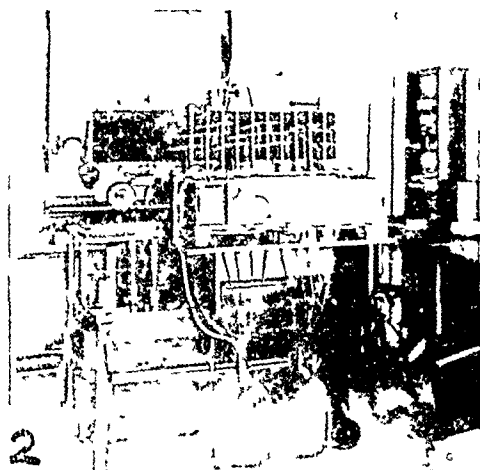
Figure 2 shows the apparatus used for testing the oxytocic activity of a solution. A strip of uterine muscle from a guinea-pig is attached to a writing lever in such a way that its contractions are recorded on the smoked paper of the kymograph. Standard Pituitrin solution is used alternately with the unknown solution until doses of each are found which will cause equal contractions of the uterine muscle. Since the strength of one solution is known, the other can then be computed. The method is prescribed in the Pharmacopoeia of the United States X, page 220, and was originally suggested by Dale and Laidlaw in 1912 (3). The apparatus (4) shown in the photograph consists of an electrically heated water bath containing twelve units, so that twelve muscles can be used simultaneously.

Figure 3 shows a similar apparatus in which six muscles can be tested at the same time.

Figure 4 shows the apparatus and method of determining the pressor activity of pituitary solutions. Dogs are deeply anesthetized with chlorotone, and then the carotid arteries are cannulated and connected to mercury manometers, which record on smoked paper. Doses of Standard Pituitrin are injected into the saphenous veins and then doses of the unknown solution are similarly injected. The dosages are varied until equal rises in blood pressure are obtained with Standard solution and unknown solution. Since the potency of one solution is known, the potency of the other can then be computed.

The technical details of the method used in this laboratory may be found in previous publications (1, 5, 6, 7).

An interesting pharmacological action of Pituitrin is the darkening of the skin of frogs and tadpoles. When a frog is exposed to bright sunlight, it becomes very much lighter in color. Then if the frog is injected with Pituitrin it turns almost black within a few minutes. Our colleague, Mr. L. W. Rowe, has demonstrated that Vasopressin produces the color change, while Oxytocin has very little effect.



The pictures illustrating this effect on the skin of the frog are omitted from this paper, as they are shown in another article in this journal (8).

It is well known that pituitary solution has a diuretic-antidiuretic action. By experiments on rabbits we have determined that it is the pressor principle that has this activity (9). In making the tests we used rabbits under urethane, amytal, chlore-tone or chloral hydrate anesthesia. Cannulas were tied into the urinary bladders and then the number of drops of urine excreted in each 5-minute interval was counted.

Figure 5 shows the results of a typical experiment with a rabbit under urethane anesthesia. In the half hour control period the urine flowed at the rate of 2-7 drops every 5 minutes.

When 0.2 unit of Pituitrin was injected there was first a short latent period or possibly a short period of suppression of urine followed by an increased excretion of urine amounting to 21 drops in 5 minutes. Then followed the antidiuretic effect so that in 40 minutes only 3 drops of urine were excreted.

When 0.2 unit of Vasopressin was injected there was a flow of urine amounting to 25 drops in 5 minutes. This was followed by the antidiuretic effect. No urine was excreted in two 5-minute periods. The antidiuretic effect was subsiding when 0.2 unit of Oxytocin was injected. This was followed by slight increase of flow of urine which may have been due to a small amount of Vasopressin in the solution—about 0.01 unit.

The injection of 0.2 unit of Pituitrin caused a gush of urine which reached the rate of 38 drops in 5 minutes and lasted for 20 minutes. The antidiuretic effect was not apparent after this injection.

The injection of 0.2 unit of Oxytocin produced very little effect.

The injection of 0.2 unit of Vasopressin on the other hand caused diuresis amounting to 29 drops in 5 minutes. This diuresis subsided so that in the course of 35 minutes the antidiuresis began to be apparent.

An injection of 0.2 unit of Pituitrin caused a gush of urine, 28 drops being excreted in 5 minutes. The antidiuretic effect appeared in 25 minutes.

Figure 6 shows another experiment similar to the first. Attention is called to the antidiuretic effect, which is apparently the first effect of injections of Vasopressin and extract of desiccated pituitaries. This early effect has been ascribed to spasm of the ureters.

Figure 7 shows the very slight effect from the injection of 0.1 unit of Oxytocin. The injection of 0.1 unit of Vasopressin, however, is followed by a considerable flow of urine, 73 drops in 5 minutes. This flow subsided in the course of 1 hour, and very little urine was excreted for the next hour.

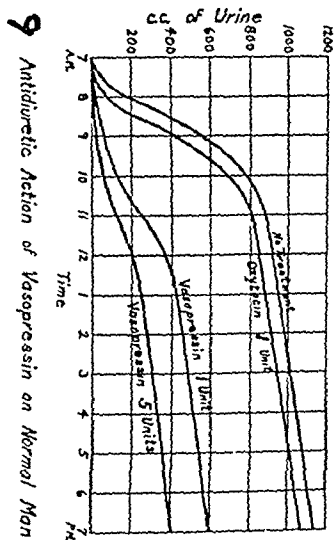
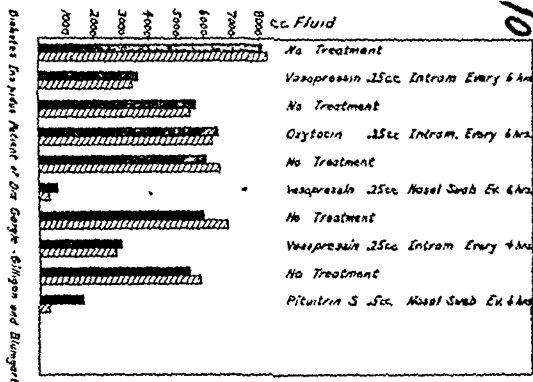
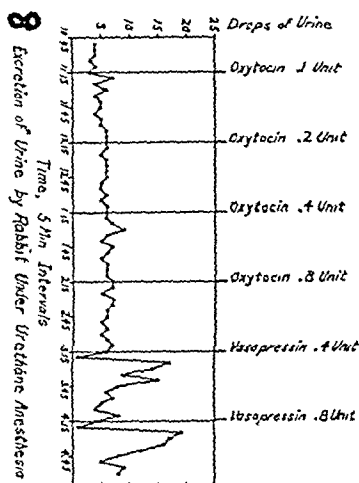
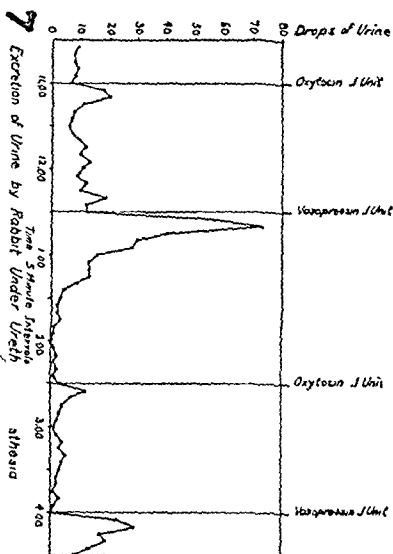
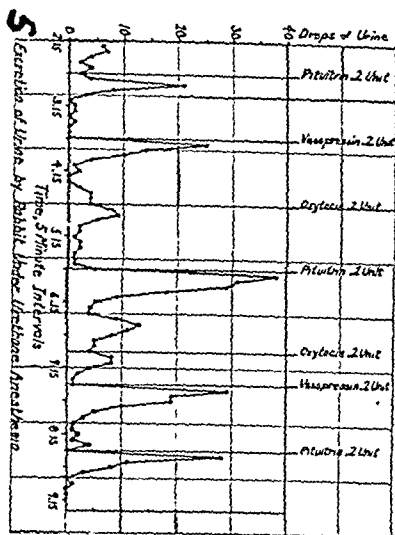
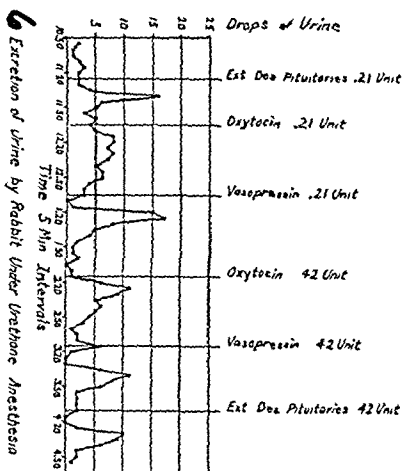




Figure 8 shows quite definitely the *lack* of diuretic-anti-diuretic action of even 0.8 unit of Oxytocin. The injection of 0.4 and 0.8 unit of Vasopressin is followed by an immediate anti-diuretic effect, followed by a diuretic effect. Probably a subsequent antidiuretic effect would have been observed if the experiment had continued longer.

In normal animals, not under anesthesia, the predominating effect of pituitary extract is the suppression of the flow of urine. This antidiuretic effect, on normal men, has been reported by Gargle, Gilligan and Blumgart (10), who found Vasopressin to have this activity, while Oxytocin had little effect. The anti-diuretic action of Vasopressin on normal men has been confirmed by Kamm in our laboratory.

Figure 9 shows the results of a typical experiment. The subject drank 1,000 cc. of water at 7 o'clock in the morning and collected urine at hourly intervals throughout the day.

In the day in which no treatment was given the total urine excreted is shown by the upper line.

On the next day 0.1 cc., or 1 unit, of Oxytocin was given by subcutaneous injection about the same time that the water was drunk. Very little, if any, effect on the urinary excretion was caused by the Oxytocin.

On a subsequent day 0.25 cc., or 5 units, of Vasopressin was given by subcutaneous injection when the water was ingested. The excretion of urine was greatly delayed and even in 12 hours only about one-half of the water had been eliminated.

On another day 0.05 cc., or 1 unit, of Vasopressin was injected about the time the water was drunk. This very small dose had almost as much antiduretic effect as did the dose 5 times as great. An intermediate dose of 3 units of Vasopressin produced an intermediate effect, not shown on the chart.

Gargle, Gilligan and Blumgart (10) have shown that Vasopressin produces the full beneficial effect of Pituitrin when administered to diabetes insipidus patients. Oxytocin was found to be devoid of this effect.

Figure 10 shows the results of the treatment. The dark areas show the amount of water ingested in 24 hours, and the shaded areas show the amount of water eliminated in the same period.

In the day without treatment the patient drank over 8000 cc. of water and passed about the same amount of urine.

On the next day 0.25 cc. of Vasopressin was given by intramuscular injection every 6 hours. The water intake was cut down to 3600 cc. and the output to a nearly equal amount.

On the next day in which no treatment was given, the water intake increased to 5600 cc. and the output was 5500 cc.

On the following day 0.25 cc. of Oxytocin was injected intramuscularly every 6 hours without any effect on the water metabolism.

A day without treatment shows about the same water intake.

On the next day when 0.25 cc. of Vasopressin was given every 6 hours by nasal application, by means of a cotton pledget, there was a great decrease in the amount of water taken in and excreted.

A day without treatment resulted in large intake of water.

Vasopressin, 0.25 cc., given intramuscularly every 4 hours again cut down the amount of water.

Pituitrin S was applied in 0.5 cc. doses intranasally by cotton pledget every 6 hours and also greatly reduced the water intake and output.

These experiments indicate clearly that Vasopressin contains the antidiuretic substance and can take the place of Pituitrin in the treatment of diabetes insipidus patients. An interesting feature of the experiments is the demonstration that intranasal application is more effective than intramuscular injections. This advantage is probably derived from the slower and prolonged absorption obtained in the intranasal administration.

Another action of Vasopressin was noted by Gargle, Gilligan and Blumgart (10) in a patient who was given an intramuscular injection of 0.5 cc. of Vasopressin. There were abdominal cramps, nausea, and diarrhea, thus indicating a stimulating effect on the gastro-intestinal musculature. This same gastro-intestinal effect has been noted by Dr. A. M. Hjort of Dartmouth College. Other investigators have given conflicting reports regarding the stimulation of the gastro-intestinal tract. Further experiments must be performed to settle the matter whether Vasopressin alone has this activity or whether Oxytocin also stimulates peristalsis, but to a lesser degree.

Vasopressin has been used by physicians in several large clinics for the treatment of diabetes insipidus, post operative shock, and the low blood pressure of Addison's disease and brain tumor, with considerable satisfaction.

Oxytocin has also been tested in some of the largest hospitals and found to cause contractions of the uterus in such a satisfactory degree that it may be used in place of Pituitrin in obstetrical practice.

## SUMMARY

The posterior lobe of the pituitary gland contains two active principles; an oxytocic principle, which causes contractions of the uterus, and a pressor principle, which raises blood pressure.

These two active principles have been separated and obtained in the form of white, stable, water soluble powders of great potency.

Solutions of these separated active principles have been recombined to form a pituitary extract identical with the original from which they were prepared, thus proving that no decomposition has taken place.

The oxytocic principle, which has been named Alpha-hypophamine, causes contraction of uterine muscle when injected into the normal animal, and contracts isolated uterine muscle when applied by contact. It is nearly free from action on other forms of smooth muscle.

The pressor principle, which has been named Beta-hypophamine, does not affect uterine muscle, but stimulates other smooth muscles. It raises blood pressure and stimulates peristalsis in the gastro-intestinal tract. It has both a diuretic and antidiuretic effect. It causes expansion of the melanophores in the skin of frogs.

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# PRONOUNCED EXOPHTHALMOS IN A CASE OF ADENOMATOUS GOITRE WITHOUT HYPERPLASIA

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Not all are agreed as to whether there is any vital difference between the thyrotoxicosis associated with an adenomatous goitre, and the hyperthyroidism of Graves' disease (exophthalmic goitre). But most authorities are willing to concede that there is a clear differentiation possible between the clinical features of these two types of goitre. It is beside the point, in this communication, to enter into any lengthy discussion of this controversy. Suffice it to state that "adenomatous goitre with hyperthyroidism" (Plummer's disease) is clinically characterized by an asymmetrical nodular enlargement of the thyroid gland in which a thrill is not palpable, and a bruit is not audible, and in which exophthalmos and the so-called thyroid eye signs (VonGraefe, Moebius, Dalrymple, Joffroy, Stellwag) are absent. Graves' disease (exophthalmic goitre), on the other hand, is typified by a symmetrical smooth, highly vascular hyperplastic gland in which a thrill is palpable and bruit audible, and in which exophthalmos and the eye signs referred to above, are present. Both syndromes include nervousness, a subjective feeling of warmth, increased perspiration, palpitation, dyspnoea, tachycardia, tremor, loss of weight and an elevated basal metabolic rate.

Exophthalmos associated with hyperplasia of the thyroid gland needs no discussion as to its frequency, but the following case is considered worthy of record because of the unusual association of exophthalmos with a toxic adenoma of the thyroid, in which careful microscopic examination failed to disclose any hyperplasia. Although it is quite possible that such a relationship has been commented upon previously, a careful survey of

the recent literature, and standard texts, discloses no such record.

A married woman, aged 41 (Case No. 129,754, University of California, Out-Patient Department, Ductless Gland Clinic), consulted us October 25, 1926. She complained of prominence of the eyes and nervousness. There was no family history of goitre and her past history was of no significance, except for the fact that she resided in Sweden until 24 years of age, and in Illinois, between 24 and 31 years of age. From 31 until the time we saw her, her residence was in Berkeley, California, a region in which the endemic incidence of goitre is negligible. Six months ago the patient's friends noticed that her eyes were becoming prominent. This ocular protrusion progressively increased. During this time she also had frequent headaches, more severe at night, and worse over the left eye.

Since the birth of her baby, 18 months before, she had been very nervous with a tendency to cry. She also experienced palpitation frequently. Perspiration was somewhat increased. The appetite, though good, was not excessive. She had lost five pounds in the previous six weeks, but this was probably related to a pan-hysterectomy for "fallen womb" and difficulty in holding urine.

The significant points in the physical examination were as follows: Her nutrition was good; skin was warm and moist; there was slight vasomotor flushing, but not the marked nervous instability ordinarily noted in Graves' disease. The exophthalmos produced an anxious and staring expression, but her demeanor was singularly placid in comparison to the agitated behavior ordinarily encountered in an individual with such pronounced exophthalmos.

The eyes were strikingly prominent, exophthalmos being greater in the left; Moebius' sign was slightly positive; Joffroy's and Dalrymple's doubtful, but Von Graefe's lid lag unmistakable. The upper lids were markedly edematous (see Fig. 1). The thyroid gland was not visibly enlarged and no thrill was palpable, nor was any bruit audible. Its consistency was firm but not nodular. The heart was not enlarged; the sounds were of good quality and only slightly "toxic." The pulse rate was 88; blood pressure, 140/80.

In short, here was a patient who exhibited pronounced exophthalmos without the usual clinical findings of Graves' disease. Moreover, from a clinical standpoint, the patient was but mildly toxic, and this was subsequently confirmed by a basal metabolic rate of only 26.5 per cent plus. In other words, the exophthalmos was out of all proportion to the relatively mild thyrotoxicosis. It therefore seemed to us unlikely that the patient could be suffering from true exophthalmic goitre (Graves' disease). It is true that mild exophthalmos sometimes persists despite considerable abatement of the toxic process, and remains then as a grim reminder of a previous wave or peak of toxicity, which has either spontaneously diminished, or been reduced by roentgen rays or thyroidectomy. The anamnesis, however, clearly demonstrated that there had been no such earlier period

of intense toxicity. Indeed the exophthalmos itself was of comparatively recent onset.

We suspected that the protrusio bulborum had some other explanation and a skiagram of the chest revealed a shadow extending one inch posterior to the sternum, suggestive of a substernal goitre. We were therefore inclined to interpret the exophthalmos as due to the pressure of this substernal goitre on the cervical sympathetic chain, and predicted that this intrathoracic extension would probably be an adenoma, since this is predominantly the type of goitre found within the thorax.



Fig 1 Patient before operation

Fig 3 Same patient four months after operation

Others on the medical service and the surgical consultants, favored the customary syndrome of exophthalmic goitre. Indeed, the opinion of the writers was regarded as rather fanciful. A subtotal thyroidectomy was done. Preliminary exploration, before resection of the gland, did not disclose any substernal extension, but just before closing, when the field was more accessible, further investigation revealed a large elongated nodule—8x3x3 cm. lying posterior to the trachea.

In view of the exceptional interest that attached to this case, especially thorough microscopic studies of the excised

tissue were made by Doctors E. I. Bartlett and R. J. Millzner. Their report follows:

*Gross pathology:* The specimen is a thyroid consisting of 4 pieces measuring, respectively, 8x3x3, 5x3.5x2, 4x3x2, and 2x1x1 cm. The total weight is 48 grams. The anterior surfaces are partly encapsulated and marked by skin clips. Other surfaces show the rough planes of resection. Cut surfaces show multiple small adenomas. In some places these are closely packed. All contain coarse colloid. The gland proper is semi-translucent with moderately divided colloid.

*Gross impression:* Multiple small, degenerating and nondegenerating adenomata of adult pattern in a normal thyroid gland.

*Microscopic pathology:* Sections of an adenoma show irregularly interspersed small to large alveoli lined by flat to low cuboidal cells and containing moderate colloid. A small amount of interalveolar epithelium is present. A few areas show separation of the alveoli by edema. Several small hemosiderin deposits from old hemorrhage are present. The gland proper shows moderate alveoli lined by flat epithelium and containing moderate colloid. The interalveolar epithelium is slightly increased. No lymphoid tissue is seen. There is an increased amount of connective tissue stroma.

*Diagnosis:* Multiple small, degenerating and nondegenerating adenomata of adult pattern in a normal thyroid gland (see Fig. 2).

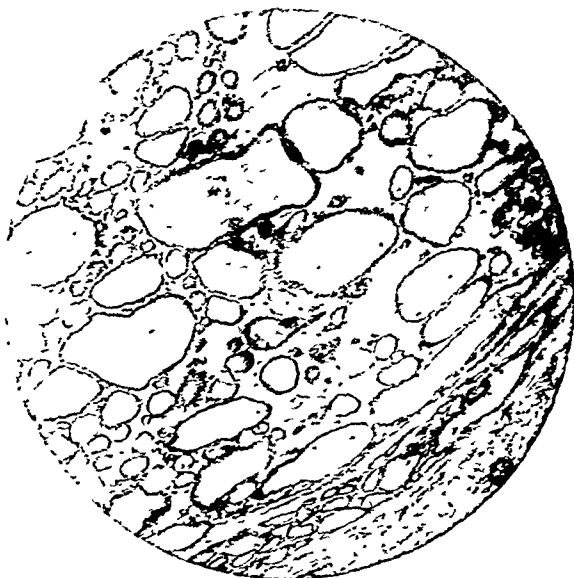


Fig. 2. Low power microscopic photomicrograph showing adenoma and adjacent thyroid gland. Gland proper at the lower right hand corner. Note the inactive cells lining the alveoli of the gland proper. The rest of the gland shows the same picture.

The patient made an uneventful recovery and one month after operation had a basal metabolic rate of 10.6 per cent plus.

The exophthalmos gradually receded, and when last seen four months after operation was scarcely noticeable (See Figure 3). The basal metabolic rate at this time was 8 per cent plus.

#### COMMENT

Exophthalmos may be due to inflammatory conditions or aneurysm within the orbit, or to intraorbital tumors; it has been noted in chronic cyanosis of the head from cerebral arteriosclerosis or aneurysm or nephritis. It may occur as a consequence of increased intracranial pressure [one of us (H. L.) has observed an outspoken case of acromegaly in which there was pronounced exophthalmus]. Finally, v. Müller mentions its occurrence as a "toxic vasomotor condition in some cases of lead poisoning." In the overwhelming majority of cases in which exophthalmos is associated with goitre, the latter is of the hyperplastic variety (exophthalmic goitre, or Graves' disease). In a smaller, but by no means negligible minority, exophthalmos occurs in connection with "mixed" goitre, which is both hyperplastic and adenomatous; although in such cases the exophthalmos has been interpreted as resulting from the hyperplastic process.

#### SUMMARY

Herewith is presented what appears to be an unusual relationship, namely, pronounced exophthalmos in a woman, consequent to the pressure of a substernal adenoma on the cervical sympathetics. The removal of this adenoma relieved the exophthalmos, and careful examination of the excised tissue failed to show any hyperplasia.

The rarity of this condition seemed to justify its publication.



# Book Reviews

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**ENDOCRINOLOGIE.** Zentralblatt für der Gebiet der innere Secretion und Konstitutionsforschung. Originale und Referate.

It is a pleasure to note the establishment of a new journal in German devoted to endocrinology and constitutional studies. Volume I, No. 1, appeared in January, 1928, under the editorship of Professors Asher and Biedl, with Professor Hans Gunther of Leipzig as managing editor. It is published by Johan Barth, Leipzig. The initial number includes 5 original articles (44 pages) and 36 pages with selected abstracts. The journal is well printed and the illustrations are notably good. The bibliographic style follows the modern usage, giving exact references. Altogether, the first issue is a credit both to the editor and to the publisher.—R. G. H.

**THE HISTOLOGY OF THE MORE IMPORTANT HUMAN ENDOCRINE ORGANS AT VARIOUS AGES.** Eugenia R. A. Cooper. Oxford University Press, American Branch, N. Y. P. 119.

Reviewed in J. Lab. & Clin. Med. 13: 1080. 1928.

**MONGOLISM. A STUDY OF THE PHYSICAL AND MENTAL CHARACTERISTICS OF MONGOLIAN IMBECILES.** Kate Brousseau, and H. G. Brainerd, 1928. The Williams Wilkins Company, Baltimore. P. 210.

The authors have compiled and analyzed the statistics relative to this disorder, adding the results of ten years of intensive personal study. The book comprises sections on "general considerations," etiology, morphology, nervous and mental characteristics, diagnosis, prognosis and treatment. The book closes with 12 illustrative case reports and a twenty-page bibliography.

All of the well known ideas as to etiology are considered and all are rejected on statistical grounds except the endocrine theory, which is found to have some dubious basis. The conclusion is reached that no known form of direct treatment is of significant value.

The material is readably presented and the illustrations, graphs and tables are clear.

HANDBUCH DER INNEREN SEKRETION. Ed. M. Hirsch, 1926. Bd. I, Lief. II. Curt Kabitzsch, Leipzig. P. 336. Jaffe, R., F. Berberich and A. W. Fischer.

In a previous issue the publication of an extensive handbook on the internal secretions by German authors was announced. The second volume of the morphological group takes up the male sex glands. Jaffe and Berberich discuss the testis in an article of 84 pages. This is based on broad study of the literature—predominately German, but considering most of the outstanding contributions in other languages. The only outstanding omissions noted are Lillie's work on freemartins and the Japanese and American work on the effects of elevated temperature on the testes. The illustrations are notably good. The somewhat extensive literature on gland transplantation receives only two pages of discussion and the effect (or lack of effect) of testis extracts practically no discussion. Pathological changes in the testis and the relation of these to other endocrine organs, on the other hand, receive detailed treatment. Students in this field will find the article valuable but needing supplementing from other sources. It is concluded that the endocrine function of the testis is mediated by the spermatic rather than the interstitial cells.

Fischer's section (50 pages), on the prostate and other accessory sex gland structures, gives an excellent summary of the morphological features and serves to emphasize the paucity of data bearing on their endocrinology. His bibliography is excellent though somewhat slipshod in form.

HANDBUCH DER INNEREN SEKRETION. Ed. M. Hirsch, 1927. Bd. I, Lief. III. Curt Kabitzsch, Leipzig. P. 472. Berberich, J. and B. Fischer-Wassels.

This volume is devoted to the morphology of the thyroid and parathyroid glands. The former is treated in a section of 95 pages by Berberich and Fischer-Wassels. It gives a conventional treatment of such topics as embryology, comparative, microscopic and gross anatomy, etc. The local thyroid reactions to various diseases is interestingly discussed. Several of the illustrations in color are excellent. The chapter gives on the whole a fairly satisfactory account of the contributions in the German literature, but is otherwise practically useless to anyone desiring an adequate discussion of the literature as a whole.

The parathyroids are treated by the same authors in much the same way in a section of 40 pages. The literature list is, however, much more satisfactory in that English, French and Italian publications receive more adequate consideration.

HANDBUCH DER INNEREN SEKRETION. Ed. M. Hirsch, 1928. Bd. I, Lief. IV. Curt Kabitzsch, Leipzig. P. 708. Jaffe, R., I. Tannenbergh and H. Josephy.

In this volume Jaffe and Tannenbergh devote a section of 188 pages to a discussion of the morphology of the adrenals. The article is illustrated with several pleasing colored cuts. As in case of other organs dealt with in this part of the work, the embryology, comparative anatomy and gross and microscopic morphology, normal and pathologic, are treated. One of the most interesting sections is that devoted to the influences of inanition, avitaminosis, toxins, etc., on the glands. The condition of the adrenals in numerous diseases is discussed. This is followed by a section on diseases of the glands themselves.

The chapter is well written and each section is summarized. The literature cited is about eighty per cent German. The bibliography is somewhat slipshod, the references being incomplete and, in some cases, translated into German.

In a section of 46 pages, Josephy discusses the normal and pathological anatomy of the vegetative centers of the mid-brain and of the sympathetic and parasympathetic nervous systems. To a considerable extent the material is dealt with on its own merits, irrespective of the endocrine glands, but, to a considerable extent, wherever any information is available, the correlation is drawn. The literature list is made up mostly of German titles.

HANDBUCH DER INNEREN SEKRETION. Ed. M. Hirsch, 1927, Bd. II, Lief. I. Curt Kabitzsch, Leipzig. P. 275. L. Asher and M. Guggenheim.

In this volume in an article of 35 pages Asher discusses the comparative physiology of the internal secretions. He takes up first the general conception of internal secretion as a physiological process. He presents an interesting classification which includes not only the hormones, but nutritive substances, harmonones and parhormones. This, of course, brings in other structures than the endocrine glands, proper. Other topics considered are methodology and comparative dynamics. Perhaps the most interesting section is that devoted to the influence of physiological factors on the action of hormones. Dregstedt's fundamental work on the influence of anesthetics in the pharmacodynamics of adrenaline is not included—presumably because of its recent appearance. The section, while by no means exhaustive, affords a judicious introduction to the general subject treated.

The section on the chemistry of the internal secretions by Guggenheim runs to 132 pages, the last 32 of which are devoted to a most excellent bibliography. Each of the recognized endo-

crine organs is taken up seriatim and such knowledge as we have on the chemistry of each is set forth with admirable clarity. In refreshing contrast to some of the authors of the volumes previously noted, Guggenheim's bibliography shows a catholic acquaintance with the literature of his subject.

In an article of 86 pages Asher discusses succinctly and excellently the usual topics treated under "Physiology of the thyroid." His bibliography, though of only 6 pages, is excellently selected to include the most significant titles in the world's literature.

The same comments can be made on his article on the parathyroids. This comprises 22 pages.

HANDBUCH DER INNEREN SEKRETION. Ed. M. Hirsch, 1927, Bd. II, Lief. II. Curt Kabitzsch, Leipzig. P. 422. Aschner, B. and W. Lahm.

In an article of 98 pages, Aschner gives a good discussion of the physiology of the hypophysis. His own interest in that topic is manifest in the relatively undue space devoted to pituitary extirpation. The discussions and the bibliography alike show familiarity with the entire significant literature. The article is necessarily incomplete, but gives on the whole as good an account of the subject as could be expected in a hundred pages.

The rest of this volume is made up of negligible discussions of the pineal gland by Aschner; of the breasts, uterus, vagina and clitoris "as endocrine organs (!)" and of the placenta, by Lahm. The article on the placenta is notably inadequate, all the significant literature except that in German having been ignored.

EL BOCIO Y EL CRETINISMO. Gregorio Marañón, 1928. Paez, Madrid. P. 189.

Marañón presents a discussion of endemic goiter and cretinism as they occur in Spain. The book is illustrated with numerous interesting photographs. The topics chiefly covered are the distribution of the disorder, together with its pathogeny and prophylaxis. The book should not be overlooked by anyone interested in the broad field of endemic goiter.

DIABETES AND ITS TREATMENT BY INSULIN AND DIET. A handbook for the patient. Orlando H. Petty, 1928. F. A. Davis Company, Philadelphia. P. 155.

This little book is an excellent compendium designed for the education of the diabetic. The fact that it has gone to a fourth

edition speaks for itself. The obscurity of diction that was noted in a few instances in the first edition has been clarified. The book can be highly recommended.

INFANCY AND HUMAN GROWTH. Arnold Gesell, 1928. The MacMillan Company, New York. P. 418.

The book includes a 28-page chapter on glandular and nutritional factors in mental growth.

THE GLANDS REGULATING PERSONALITY. A STUDY OF THE GLANDS OF INTERNAL SECRETION IN RELATION TO THE TYPES OF HUMAN NATURE. Louis Berman, 1928. Second Edition, Revised. The MacMillan Company, New York. P. 329.

The following excerpts represent the central theme of this book:

"The life of every individual, in every stage, is dominated largely by his glands of internal secretion. That is, they, as a complex internal messenger and director system, control organ and function, conduct and character. The orderliness of human life, in the sequential march of its episodes, crises, successes and failures, depends, to a large extent, upon their interactions with each other and with the environment.

"One or several of the glands possesses a controlling or superior influence above that of the others in the physiology of the individual, and so becomes the central gland of his life, its dominant, indeed, so far as it casts a deciding vote or veto, in its everyday existence and incidents as well as in its high points, the climaxes and emergencies.

"These glandular preponderances are determining factors in the personality, creating genius and dullard, weakling and giant, Cavalier and Puritan. All human traits may be analyzed in terms of them because they are expressions of them.

"Specific types of personality may be directly associated with particular glandular prominence, so that we have the thyroid-centered type, the pituitary-centered type, the adrenal-centered types, etc. These are the prototypes in their purity most easily described and recognized.

"Gay vivacity and grim determination, the temperament of a Louis XIV and the soul of a Cromwell, are the crystallizations of these chemical substances acting upon the brain."

Excellent entertainment—brilliant speculation—mostly exaggerated, but harmless if one does not swallow it whole. The unfortunate aspect of this book consists in the appeal that it

will have for the laity. Imaginative theorizing becomes dangerous when expressed as if it were established fact.

THE ENDOCRINES IN GENERAL MEDICINE. A. Langdon Brown, 1927. Paul B. Hoeber, New York. P. 134.

Reviewed in Arch. Int. Med. 42: 148-149. 1928.

METHODS OF BIOLOGICAL ASSAY. J. H. Burn, 1928. Oxford University Press. P. 126.

The book contains descriptions of methods of biological assay of pituitary (posterior lobe) extract, insulin, adrenalin, ovarian œstrus-producing hormone, parathyroid hormone, thyroid extract and anterior lobe of the pituitary gland.

INNERE SEKRETION IN DER ERSTEN LEBENSZEIT (vor und nach der Geburt). Thomas, E. 1926. Gustav Fischer, Jena. Pp. 194.

# Abstract Department

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The comparative effect of epinephrin upon blood pressure and intestinal motility in the dog. Dragstedt, C. A. and J. W. Huffman. *Am. J. Physiol.* 85: 129. 1928.

The simultaneous effects of continuous injections of epinephrin on blood pressure and intestinal motility were recorded in dogs during and after anesthesia with ether, under morphine, under paraldehyde, and in the absence of drugs and anesthetics. It was found that with a certain amount of ether and in three instances with barbital, trional and amytal the blood pressure would be raised at the expense of intestinal motility. In normal animals and in dogs under morphine, paraldehyde or after stunning, the opposite relationship obtains. In these conditions considerable rises in blood pressure can be obtained without intestinal inhibition.

—Authors' Abst.

The blood pressure of adrenalectomized rats. Durant, R. R., *Am. J. Physiol.* 85: 364. 1928.

The adrenals were removed from 20 female rats, approximately two years old and varying in weight between 157 grams and 400 grams. The blood pressure of 11 of these animals determined by the direct method within the first 5 hours following the operation varied considerably with extremes of 85 mm. and 145 mm., and an average of 112 mm. Hg. The last figure has been found previously to be the average pressure for normal rats of the same age. The blood pressures of the remaining 9 animals, determined 6 hours to 22 days after the extirpation, were low, with a minimum of 52 mm., a maximum of 95 mm., and an average of 77 mm. Hg. Ten animals of the same age and of both sexes were operated as controls. Two had one adrenal removed, another had one whole capsule and all but a small piece of cortex of the other removed. A sham operation simulating the adrenalectomy was performed upon the remaining seven. The pressures of this group were found to vary between 65 mm. and 135 mm., with an average of 104 mm. Hg. Eliminating the data obtained upon 2 animals, which at autopsy proved to be in very poor condition, the average pressure for the control group is 111 mm. Hg. The three animals that had undergone partial adrenalectomy possessed the normal pressure. These observations indicate that in rats adrenalectomy has no immediate effect

upon blood pressure, but that after 6 hours a marked fall in pressure occurs and that the adrenals through either their cortical or medullary components are concerned in the maintenance of normal pressure.—Author's Abst.

**The action of epinephrin upon the capillaries and fibers of skeletal muscle.** Hartman, F. A., J. I. Evans and Helen G. Walker. *Am. J. Physiol.* 85: 91-98. 1928.

Seventy cats of various ages and 2 rabbits were studied while under the influence of ether, urethane or else decerebrated. The microscopic changes of either the sartorius of the tibialis anticus were observed with transmitted light. Adrenalin ranging from 0.2 cc. of 1:100,000 to 1 cc. 1:10,000 was injected into the jugular vein. Ether caused a marked dilatation of the capillaries, an increase in blood flow and haziness of the field. Adrenalin caused dilatation of capillaries, venules, arterioles, veins and arteries, and an increase in blood flow with small doses. Later congestion and a slower rate of flow might occur. The whole field became clearer and brighter. Cross striations in the muscle fibers became visible or better defined. Also transverse twitching or vibration of the muscle fibers might appear. These effects lasted as long as seven minutes. With larger doses (1 cc. or more of 1:100,000), the capillaries and very small vessels dilated as before, while the veins, arteries and arterioles constricted. The transparency and twitching became more marked. Muscle denervated only a few hours shows little change in the capillaries in response to adrenalin because dilatation is already great. If several days elapsed after denervation, the adrenalin reaction resembled that in the normal, except that it was unstable. Adrenalin twitching was absent or poorly developed.

—Authors' Summary.

**Suprarenal insufficiency: Report of two cases.** Marsh, H. E., *Am. J. M. Sc.* 175: 769-777. 1928.

A biographical sketch of Addison is given and a survey of his investigation of the disease which bears his name. Two cases are presented which clinically conform to Addison's disease. Both patients improved under substitutional therapy and are still living. Both had recurrence of symptoms whenever treatment was discontinued.—Author's Summary.

**Rat activity and adrenalin.** Nice, L. B., D. S. Greenberg and S. L. Greenberg. *Am. J. Physiol.* 85: 397. 1928.

The activity of three groups of rats was studied. A normal group was given 1 cc. of 1:50,000 adrenalin chloride hypodermically daily; to a second group of adrenalectomized rats was administered an equal amount of adrenalin in the same way, while a third group of adrenalectomized rats was not injected. The spontaneous



activity of the normal rats was decreased on the whole, while the activity of the injected adrenalectomized rats closely paralleled that of the non-treated group.—Authors' Abst.

**Adrenal insufficiency:** The beneficial influence of cortical adrenal extracts in adrenalectomized animals. Rogoff, J. M. and G. N. Stewart, *Am. J. Physiol.* 85: 404. 1928.

Administration of adrenal cortical material prepared by extraction, in various ways and with various solvents, is capable of prolonging life of completely adrenalectomized animals well beyond the maximum period of survival of control, untreated adrenalectomized animals. In animals which do not live beyond the maximum period of survival of adrenalectomized, untreated controls, as well as those which exceed this period, the usual symptoms are generally ameliorated.—Authors' Abst.

**Effect of haemorrhage upon the rate of liberation of epinephrine from the suprarenal gland of dogs.** Saito, S., *Tohoku J. Exper. Med.* 11: 79-115. 1928.

Experiments were made on 8 control dogs, on 16 anesthetized and on 11 de-afferented dogs. Adrenal blood was collected in vena cava pockets and assayed by means of the rabbit intestine method. It was found that with the dogs under ether the loss of  $1/5$  of the total quantity of blood called forth a small but definite augmentation in the secretion rate of adrenalin. The bleeding of  $1/10$  was not certain to cause the hypersecretion of epinephrine. In the experiments on the non-fastened, non-anaesthetized de-afferented dogs the loss of  $1/15$  of the total blood quantity was usually effective in evoking the increase, though weak, of epinephrine discharge. When  $1/10$  of the whole blood was lost, the velocity of liberation two to ten times as rapid as the initial was invariably noted, and the hypersecretion continued for about three hours. When  $1/3$  or  $2/5$  of the total amount was shed, the output rate ten to thirty times as quick was noted, and the hyperactivity of the medulliadrenal gland lasted for a considerable length of time. At the fourth or sixth hour after the bleeding the epinephrine secretion had a definitely exaggerated velocity. In general, the greater the haemorrhage, the greater and the longer the hypersecretion of epinephrine from the suprarenal capsule. For the material difference between the two sets of experiments above mentioned the narcosis is responsible, at least chiefly.—R. G. H.

**Studies on the conditions of activity in endocrine glands. XXIV. Asphyxial stimulation of the denervated adrenal gland.** Zwemer, R. L. and H. F. Newton, *Am. J. Physiol.* 85: 507-511. 1928.

Asphyxia of the denervated adrenal, induced by compression of the aorta near the diaphragm for ten seconds was found in 7

cats to cause a discharge of adrenin, as shown by a large increase in the rate of the denervated heart. Demedullation of the adrenal prevented the increase in heart rate after asphyxia. It was concluded, therefore, that the denervated adrenal medulla can still respond to asphyxial stimulation.—R. G. H.

**The function of the carotid body.** Relation to the carotid sinus reflex (*Sur la fonction de la glande [paraganglion] carotidienne. La glande et le réflexe du sinus carotidien*). Jacobovici, J., I. Nitzescu and A. Pop, *Compt. rend. Soc. de biol.* 98: 640-643. 1928.

Hering has described a reflex fall of blood pressure following pressure in the region of the carotid sinus. Experiments in five cases on man indicate that this reflex is due to stimulation of the carotid body (glomus caroticum).—J. C. D.

**The peripheral control of blood sugar by drugs** (*Die periphere Steuerung der Blutzuckerregulierung auf Gifte*). Bertram, F., *Arch. f. exp. Path. u. Pharmacol.* 126: 267. 1927. *Abst., Physiol. Absts.* 13: 174.

The effect of various agents on the blood sugar is fully reviewed. Calcium, acids, and thyroid preparations increase the hyperglycaemia due to adrenaline or food, and diminish hypoglycaemia due to insulin. Potassium and alkalis have the reverse effects. None of these agents has per se much effect on the normal blood sugar. On the other hand, the hyperglycaemia due to pilocarpin is increased by potassium and lowered by calcium. It is also, however, increased by acids and thyroid.

**Calcium metabolism in skin diseases.** Burgess, N., *Brit. J. Dermat.* 40: 279. 1928. *Abst., J. A. M. A.* 91: 525.

The discovery made by Burgess of a normal figure for the total serum calcium in association with a diminished amount of precipitable calcium in many cases, and a diminution of both total and precipitable calcium in a few cases of certain skin diseases, confirms the work of Vines and Grove. Cases of urticaria, especially those showing marked dermatographism, prurigo of the Besnier type, total alopecia areata, light sensitization of the adult type, and eczema, in the vast majority of instances present a marked diminution of precipitable serum calcium. Cases of acro-asphyxia and erythema pernio can be divided into two groups—those showing a greatly diminished precipitable calcium, and those in which the serum calcium is normal. Cases of urticaria, prurigo, eczema and those cases of acro-asphyxia and chilblains with a low serum calcium were considerably improved by treatment with calcium and parathyroid. Only one case of sporiasis showed a diminished precipitable serum calcium. Two patients with seborrheic dermatitis out of five had a

lowered serum calcium, accompanied by much secondary infection. A slight diminution of the serum calcium was found in one case of erythema multiforme, while normal figures were obtained in a case of Darier's disease and a case of acrodermatitis continua. Of the cases investigated, those in which the endocrine glands and sympathetic nervous system are believed to be primarily at fault showed a diminution of the precipitable calcium in the serum, while in most cases the total calcium was found to be normal. It is believed that the dysfunction of the endocrine glands leads to an alteration in the chemical or physical state of the calcium in the serum, so that there is a diminution in the amount of calcium which can be used by the tissues. This is believed to cause an increased irritability of the sympathetic nervous system which leads to the formation of skin lesions.

**Testicular grafts in Triton.** Fresh experimental evidence that the sex cells do not control secondary sex characteristics (*Greffes testiculaires chez les Tritons. Nouvelle preuve expérimentale du fait que les cellules de la lignée séminale n'exercent aucune action sur les caracteres sexuels*). Aron, M., *Compt. rend. Soc. de biol.* 98: 845-847. 1928.

In this urodele the sex cells, spermatogonia, and Sertoli cells develop first and later, into spaces made vacant by discharge of spermatazoa, grow glandular cells corresponding to the interstitial cells of mammals. Animals were castrated and then grafted with testes from other Tritons. In a number of cases these animals developed normally, while others showed no secondary male characters. In the first group, autopsy showed that the grafts had made connections with the duct system; that spermatazoa had been discharged and the interstitial gland had developed. In the latter no connection had been made, the spermatazoa and other cells of the testes were present, but the development of the interstitial gland had been inhibited and it was absent. It is the interstitial gland cells, not the sex cells, which control the secondary sex characters.  
—J. C. D.

**Influence of castration on metabolism (both basal and maximum)** (*Action de la castration sur le métabolisme énergétique [Métabolisme de base et métabolisme de sommet]*). Chahovitch, X. and Mlle. M. Vichnjitch, *Compt. rend. Soc. de biol.* 98: 1153-1155, 1928.

Castration reduces the metabolic rate in rats.—J. C. D.

**The clinical use of ovarian follicular hormone with special reference to functional sterility.** Hirst, J. C., II, *Am. J. Obst. & Gynec.* 15: 487. 1928.

In 5 of 12 cases of sterility, conception occurred after a course

of injection of ovarian follicular hormone. Three of 5 subjects with menstrual disorders were benefitted by the hormone.

—M. O. L.

**The effect of injection of follicular extract on the sex organs in guinea pig and interaction between follicular substances and substances given off by corpus luteum.** Loeb, L. and W. B. Kountz. *Am. J. Physiol.* 84: 283-306. 1928.

Injections of follicular extract in immature guinea pigs accelerate the maturation of follicles; similarly in under-fed guinea pigs, they delay the hypotypical state of the ovaries or diminish the intensity of this process and thus allow the better development of the follicles as compared to the condition in undernourished, but not injected, controls. Otherwise injection of follicular extract does not accelerate noticeably the maturation of follicles or to increase the number of mature follicles. Injection of follicular extract prevents ovulation in the guinea pig and must therefore lead to sterility as long as the injections are continued. The large, persistent corpus luteum, as it exists in hysterectomized and pregnant animals, tends to counteract the acceleration effects of the injections on the opening of the vagina and the proliferation of the vagina under the influence of the injections. These investigations thus confirm and bring out still more definitely the difference in the effects of the large, persistent corpus luteum on the one hand and of the small cyclic corpus luteum on the other hand. The injections of follicular extract have in general only very slight effects on the uterus of the guinea pig; they cause hyperemia, slight local edema and some hemorrhage of the mucosa; in a few cases marked oestral changes in surface epithelium, neck of the glands and connective tissue were observed. Neither does the follicular substance cause the predecidual proliferation or the uterine mucosa, which is produced by the corpus luteum at a certain phase of the normal cycle, but on the contrary, it tends to prevent this effect. On the other hand, the corpus luteum does not cause the proliferation of the vagina which is called forth by the follicular substance; it tends rather to prevent this effect. It is concluded that the ovarian follicles and corpus luteum contain or give off substances which are not identical. Some of the effects of these substances on the sex organs are different, while others are similar.—Authors' Summary (abbreviated).

**Experiments on isolated ovaries (Versuche an isolierten Eierstöcken).** Nikolaeff, M. P., *Ztschr. f. d. ges. exper. Med.* 54: 32-57. 1927. *Abst., Biol. Absts.* 1: 1059.

In specimens of cow's ovary and broad ligament from the abattoir, the ovarian artery and vein were cannulated, collateral vessels ligated, and the ovary perfused with oxygenated Ringer-Locke solution at body temperature. The perfusate was collected and tested

pharmacologically. During perfusion the broad ligament undergoes periodic spontaneous contractions, varying in type in the pregnant and non-pregnant cow. The perfusate, at first slightly acid, becomes neutral as perfusion is continued, and contains a small amount of protein. It usually increases the amplitude of contractions of the isolated frog's heart, while slowing the rhythm; and usually raises the blood-pressure of dogs. In low concentration this fluid raises tonus and increases contractions of isolated cat's intestine; concentrated dosage gives an opposite effect. On the isolated cat's uterus it acts strikingly, increasing tonus and giving the contractions a tetanic character. Release of adrenalin-like substance from the isolated adrenal is increased by the ovarian perfusate.

**The influence of prostatectomy on the sex life of the male albino rat.** Patterson, T. L., *Am. J. Physiol.* 85: 398. 1928.

Removal of both the seminal vesicles and the prostate from male rats produces absolute sterility, but it has not been determined if sterility follows complete prostatectomy alone. Young male rats prostatectomized at five to six weeks of age, mated with normal females, and observed over a period of twenty months were sterile, but this only occurs when the extirpation of the gland is complete, as evidenced by histological studies. The sexual instincts and sexual activity develop in these animals normally, though with some delay, which is probably due to operative interference in a region very sensitive to injury. This indicates that the development of the somatic sex characters and of the psycho-sexual behavior is independent of the presence of the prostate and of any endocrine function of this organ.—Author's Abst.

**Extraction of ovarian hormone from urine.** Veler, C. D. and E. A. Doisy. *Proc. Soc. Exper. Biol. & Med.* 25: 806-807. 1927-28.

Description of the procedure used in the extraction of the ovarian hormone from urine. From 500-1,200 rat units per liter were obtained from the urine of pregnant women. Post-partum urines contain very little of the hormone 48 hours after delivery.

—E. A. Doisy.

**Consequences of castration and of eunuchoidism in man (Beiträge zur Kenntnis der Kastrationsfolgen und des Eunuchoidismus beim Mann).** Wagenseil, F., *Ztschr. f. Morphol. u. Anthrop.* 26: 264-304. 1927. Abst., *Biol. Absts.* 1: 1067.

Observations were carried out on 11 eunuchs (natives of Sudan and Abyssinia) castrated at the age of 7-12. In most cases even the external genitalia were removed. Two eunuchs died of typhus and were used for histological studies. The author considers the gonads necessary for the onset of puberty, either directly or perhaps through other glands of internal secretion, but his pathologic-

anatomical findings do not seem to support the latter contention. Changes were noted only in the hypophysis, which showed eosinophilia, and in the thymus, the epithelial parts of which underwent hyperplasia. The thyroid was generally reduced in size. In a tall eunuch the x-ray picture revealed a large sella turcica, indicating an enlargement of the anterior lobe of the hypophysis. The author cannot confirm Koch, who believes that age at castration is important in the differentiation of various types of eunuchs, and thinks that the reactions of the ductless glands to castration vary with the individual; also he does not believe that the adiposity of eunuchs is always due to pituitary involvement. He agrees with Faltz, who differentiates between pituitary and genital dystrophia adiposo-genitalis, and believes that the adiposity is due solely to the absence of the internal secretion of testes. The author autopsied and examined histologically a eunuchoid Turk. Testicles and other genitalia, heart, and appendix showed embryonic characteristics. He regards eunuchoidism as of idiopathic origin, being closely related to or identical with infantilism. Symptoms of eunuchoidism are ascribed to a hypofunction of the gonads, and there is believed to be no evidence that the hypophysis is responsible.

**On bitemporal contraction of the visual field in pregnancy.** Abramowicz, I., *Brit. J. Ophth.* 11: 17-27. 1927. *Abst., Biol. Absts.*, 1: 1060.

In few cases of normal pregnancy (6 per cent) there occurs in the last month of pregnancy a slight temporal contraction of the visual field, which may be occasioned by the hypertrophy of the pituitary body. On the tenth day after delivery the visual field returns to normal.

**Diuretic-antidiuretic effect of the pressor principle of the posterior lobe of the pituitary gland.** Bugbee, E. P. and A. E. Simond. *Am. J. Physiol.* 85: 357. 1928.

It has been demonstrated that the posterior lobe of the pituitary gland contains two active principles, one which contracts uterine muscle and the other which raises blood pressure. We were interested in finding out if the diuretic-antidiuretic effect is associated with one of these or is due to still another active principle. Experiments have been made on rabbits under urethane, amytal, chloralhydrate and chloretone anesthesia. It was found that the oxytocic principle has little effect upon the flow of urine, determined by counting the drops falling from a cannula in the bladder. The pressor principle causes first a decrease in urine flow, then a copious flow of short duration, followed by diminished excretion. The relative intensity and duration of these three effects vary in different rabbits and depend upon the depth of anesthesia and upon the dosage of pressor principle. Renal function tests on rabbits have been made in a manner similar to the commonly used clinical

phenolsulphonephthalein test. It has been found that the oxytocic principle has little effect upon the excretion of dye, whereas the pressor principle diminishes the rate of excretion of the dye.

—Authors' Abst.

Posterior pituitary lobe extract: its action on water excretion in normal cases, cases with diabetes insipidus, and cases with sclerotic kidneys (*Action de l'extrait du lobe posterieur de l'hypophyse sur le metabolisme de l'eau, chez l'homme normal, dans le diabete insipide et la sclerose renale*). Coelho, E., *Compt. rend. Soc. de biol.* 98: 469. 1928.

Subcutaneous injections always reduce the output of urine.

—J. C. D.

The antidiuretic effect of the oxytocic and pressor principles of the extract of the posterior lobe of the pituitary. Gargle, S. L., D. R. Gilligan and H. L. Blumgart. *New England J. of Med.* 98: 169. 1928.

Kamm has recently separated the extract of the posterior lobe of the hypophysis into two parts. Oxytocin has an oxytocic action and vasopressin a pressor action. The authors summarize their clinical studies as follows: In four normal men, single doses of vasopressin checked the excretion of a liter of water for five or six hours, while oxytocin had but slight effect. In two patients with diabetes insipidus, vasopressin effectively controlled the thirst and polyuria, while oxytocin proved ineffective. Intranasal administration of vasopressin by cotton pledget proved more effective than subcutaneous administration in the two patients with diabetes insipidus. On the basis of these findings the antidiuretic effect of extracts of the posterior lobe of the pituitary gland seems to be inherent in the pressor principle.—J. C. D.

The active principles of the posterior lobe of the pituitary gland. I. The demonstration of two active principles. II. The separation of the two principles and their concentration in the form of potent solid preparations. Kamm, O., T. B. Aldrich, I. W. Grote, L. W. Rowe and E. P. Bugbee, *J. Am. Chem. Soc.* 50: 573. 1928.

A substantially complete separation of two active principles of the posterior lobe of the pituitary has been accomplished by the employment of salting-out methods and, subsequently, by use of appropriate solvents and precipitants. One of these active principles raises blood pressure and the other stimulates contraction of uterine muscle. Solutions of these separated active principles have been recombined to form a pituitary extract identical with the original from which they were prepared, thus proving that no decomposition has taken place. The substantially pure pressor principle (beta-hypophamine) has been obtained in the form of a white, stable, wa-

ter-soluble powder 80 times as potent as the International Standard Powdered Pituitary. The separated oxytocic principle (alpha-hypophamine) has been observed in the form of a white, stable, water-soluble powder which is more than 150 times as potent as the International Powdered Pituitary. The pressor principle has been shown to be responsible for the diuretic-antidiuretic action of pituitary extracts. The pressor principle when tested on animals for demonstration of pressor effects shows the development of tolerance which is characteristic of active pituitary extracts. It has been shown to possess no appreciable depressor action. Both active principles are basic bodies, presumably amines. Practical manufacturing methods have been developed for the separation of these two hormones, and they have been made available to the medical profession for careful clinical trial.—M. O. L.

**Röntgen-ray treatment of pituitary tumors.** Sharapov, B. I. and V. I. Jutchenko. *Physiotherapia*, 2: 80. 1927. *Abst., J. A. M. A.* 91: 136.

Sharapov and Jutchenko report the results obtained with roentgen-ray treatment in forty-nine cases of tumors of the pars anterior of the hypophysis, characterized by more or less prominent symptoms of acromegaly. The first beneficial effect noted is the disappearance or diminution of symptoms due to pressure on the chiasma, enlargement of the field of vision and improvement of vision. Symptoms of increased brain pressure, headaches and vomiting are improved or disappear. At a later date, there is a return of the sexual function, manifested in women by the return of menstruation, in men by the return of potency. Coincident with this is a loss in weight. The enlarged extremities do not return to a normal state, but a relative diminution in size was observed in some of the cases. Apparently adenomas only are destroyed by the rays. Teratomas, cysts and gummas do not yield to the treatment. In the beginning there may be an exacerbation of symptoms, which, however, should not deter one from continuing the irradiations.

**Study of a substance in desiccated tissues which increases sugar utilization more than insulin.** Burge, W. E., A. M. Estes and G. C. Wickwire. *Am. J. Physiol.* 85: 357-358. 1928.

The effect on sugar utilization of a great number of substances, such as the optically active and optically inactive amino acids, aminoids, ovarian and testicular substances, insulin, pituitrin, thyroxin, adrenalin, alcohol, inorganic salts, ether, chloroform, nitrous oxide and ethylene, has been studied. This investigation is concerned particularly with the effect of commercially prepared desiccated tissues, such as aminoids, a commercially prepared meat digest with an amino nitrogen of 7.5 per cent amino acids, desiccated testicular and ovarian substances. One hundred milligrams of each of these



materials, as well as varying amounts of insulin, were added to 100 cc. of a 0.1 per cent dextrose solution in beakers. Two gold fish, with a combined weight of five grams, were introduced into each of the beakers and air was kept bubbling through the liquid to insure an adequate supply of oxygen. Sugar determinations were made immediately and after thirty hours. It was found that the aminoids produced a greater increase in sugar utilization than the amino acids taken singly or collectively. The desiccated ovarian and testicular substances greatly increased sugar utilization. Desiccated thyroid increased sugar metabolism, while thyroxin did not. Insulin increases sugar utilization, but to a less extent than the desiccated tissues. The view is advanced that none of these desiccated tissues per se increases sugar utilization, but that they contain a substance which is responsible for the stimulating effect on sugar metabolism.

—Authors' Abst.

Insulin does not increase the binding power of blood cells for glucose. Refutation of this theory of glycemia (*L'Insuline n'augmente pas la fixation des glucides sanguins par les globules. Refutation de la notion de glycémine*). Fontès, G. and L. Thivolle. *Compt. rend Soc. de biol.* 98: 847-849. 1928.

Loewi and others regard the blood sugar balance as determined by "glycémine," a substance arising in the liver and causing glycemia, and insulin. The test for the relative amounts of these substances is based on the supposed increased binding power for glucose of the blood cells in the presence of insulin. This paper gives extensive tables from observations on man and other animals showing that insulin does not influence the blood cells in this way.

—J. C. D.

Latent tolerance in diabetes mellitus. Gibson, R. B., *Am. J. Physiol.* 85: 375. 1928.

Diabetics desugarized on maintenance diets with a F. A.: G. of 1.5 and the required insulin have shown remarkable improvement following high sugar ingestion with increased insulin. Two to three days of high sugar ingestion, with intervals of routine management in series, increases the tolerance until dietary management without insulin may suffice to control the diabetes; the most severe cases may require a greatly diminished insulin dosage. The procedure is especially effective in younger patients.—Author's Abst.

Hypertension and diabetes. Kramer, D. W., *Am. J. M. Sc.* 176: 23-31. 1928.

The frequency of hypertension in diabetes is more common than we have been led to believe. In this study of 500 consecutive cases of diabetes, 195 patients (39 per cent) showed a blood pressure of 150 mm. mercury or above. The presence of hypertension in

diabetics may be attributed to various factors: the pathogenesis of these conditions is practically the same, and they are apt to appear in those past middle life, the highest percentage occurring in the sixth decade. This was evident in both series, 36.2 per cent in the diabetic group, and 39.1 per cent in the hypertensive non-diabetic group. Individuals with persistent hypertension of the non-nephritic type may in time develop diabetes. It is unlikely that diabetes, through its hyperglycemia, produces hypertension.

• —Author's Summary.

**The absorption of insulin from Thiry Vella fistulae in normal and depancreatized dogs.** Murlin, J. R. and Ruth E. Latta. *Am. J. Physiol.* 85: 397. 1928.

The results indicate that fistulae prepared several months before being used for experiments with insulin absorb the hormone better than freshly prepared fistulae. Weak alkalis up to 20th normal favor absorption. Weak HCl up to 100th normal does not retard absorption, but greater strength does in most of the tests. Blood serum retards the destruction of insulin by pepsin-HCl. This is due to the buffering effect of the serum proteins on the acid. When acid stronger than N/40 is used with ox-blood serum, there is destruction of insulin by pepsin. Blood serum alone or serum and HCl up to N/70 does not prevent destruction of insulin by trypsin.—Authors' Abst.

**Large ulcers of the leg of fourteen years' duration healed within twenty days with insulin pomnade** (*Vastes ulcères de jambe dantant de 14 ans et guéris en 20 jours par la pomnade à l'insuline*). Pautrier, L. M. and Mlle. Ullmo. *Presse méd.*, 36: 58. 1928.

The authors call attention again to the treatment of ulcers of the leg with insulin. The work comes from the skin clinic at Strasbourg. The patient was 64 years of age with a glycemia of 1200 mgm. per 100 cc. and had had these ulcers for the past 14 years. The ulcers cicatrized completely in 20 days following the use of insulin paste.—H. J. J.

**Difficulties in diagnosis of insulin coma.** Sevringhaus, E. L., J. A. M. A. 91: 305-307. 1928. Abst., A. M. A.

The author reports two cases of diabetes mellitus as examples of the difficulties that may occur in the diagnosis of coma due to an excess of insulin. They illustrate the necessity for the diagnosis of the cause of coma by clinical observation and the simplest laboratory aids, such as tests for urine sugar and acetone. They also call attention to the necessity for a therapeutic test to decide the presumptive diagnosis when the insulin reaction is not of the usual type, with sweating and hunger. When there is doubt as to the nature of a coma in a diabetic patient, there is nothing to be lost and much

to be gained from the therapeutic test of an intravenous injection of from 10 to 20 cc. of 50 per cent dextrose. This is so readily available in sterile form, and can be given with such ease, that it should always be at hand. In insulin coma it has repeatedly given results in from one to three minutes. The diabetic comatose patient will not respond, nor can any further harm be done by the single injection. If the coma does not respond to the dextrose within at least ten minutes, it would then be safe to proceed with the usual measures for treatment of true diabetic coma. Insulin coma yields quickly to intravenous injections of dextrose unless there is a complicating factor. The two cases presented illustrate the manner in which nervous excitement, unaccustomed exercise, or omission of food usually eaten, may induce severe reactions when they are not otherwise expected. The diagnosis was made uncertain because of suspected cerebrovascular syphilis in one case and the fear of a developing meningitic infection in the other. The therapeutic test of administering dextrose intravenously for relief of coma which may be due to insulin should be made.

**Acromegaly and diabetes.** Yater, W. M., Arch. Int. Med. 41: 883-912. 1928.

A brief summary of the results of the main experimental and clinical investigations on the question of the relationship of the pituitary gland to carbohydrate metabolism has been given. Six more cases have been recorded of the interesting combination of acromegaly and diabetes mellitus, in 3 of which insulin was required. In one of these cases the diagnosis of acromegaly is admittedly questionable. Four others of a series of 79 cases of acromegaly showed some disturbance of carbohydrate metabolism, but this feature was not carefully studied in them. The diabetes in the 6 cases reported was in all essential respects similar to the ordinary form and responded similarly to diet and insulin therapy. Three of the patients presented the unique complication of increased basal metabolic rate, in all three of whom it was presumably due to hyperthyroidism.—Author's Summary.

**Relation of parathyroidectomy to voluntary activity in the white rat.** Durrant, E. P., Am. J. Physiol. 85: 364. 1928.

Observations by means of revolving activity cages on both unilaterally and bilaterally parathyroidectomized rats, 90 to 100 days old, show that though tetany is equally pronounced after both operations, the activity is merely temporarily depressed; but the recovery is much more rapid following the unilateral ablation. In rats 200 to 210 days old the results are the same qualitatively, but are more variable in amount.—Author's Abst.

**Vater Pacinian corpuscles in the parathyroid glands of guinea pigs**  
(Sur l'existence de corpuscles de Vater-Pacini dans les glandes

12 to 20 days, but all the thyroid-fed animals grew less rapidly than their litter controls; the former showing an increase of weight of 12 per cent to 480 per cent, the latter an increase of from 75 per cent to 675 per cent.—Author's Abst.

**Childhood myxedema.** Gordon, M. B., *Am. Med.* 23: 30-36. 1928.

A resume of the present knowledge on the subject is given, and the use of the term "childhood myxedema" is advocated, instead of "sporadic cretinism." The condition which is called sporadic cretinism in this country is not the same condition recognized as cretinism in Europe, and since it differs pathologically and clinically, it should be considered as a separate clinical entity. The condition in America is really an exaggerated and intense form of hypothyroidism. It seems advisable to dispense with the term sporadic cretinism, at least as far as it applies to the condition as it exists in America, and to restrict the term cretinism to the endemic type found in Europe and Asia. Thyroid disorders due to a deficiency in thyroid function are classified according to the following groupings: (1) Endemic cretinism; (2) childhood myxedema (congenital myxedema, infantile myxedema, juvenile myxedema); (3) adult myxedema; (4) post-operative myxedema; (5) hypothyroid states in childhood.

**Psychosis and hyperthyroidism.** Johnson, W. O., *J. Nerv. & Ment. Dis.* 67: 558. 1928.

A report is made of observations on 2286 goiter cases operated in the Cleveland Clinic Hospital, 1925-26. A comparison is made between the acute maniacal confusional states of acute thyrotoxicosis and 24 cases of true psychosis. A brief review of the literature is given. The low incidence of true psychosis in thyrotoxic conditions is shown, and it is also shown that in the true psychosis there is personal or family history of psychosis before the goiter develops. Hallucinations and delusions, with predominance of depressive states, is the rule. Operation in these conditions does not cure, in contrast to the thyrotoxic maniacal confusional states. These, if diagnosed and treated before they reach delirium, can be cured.—Author's Abst.

# Endocrinology

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STUDIES OF THE ENDOCRINE GLANDS  
VI. PLURIGLANDULAR SYNDROMES

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In a series of previous communications the details of an objective method for the differential diagnosis of endocrine disorders have been reported (1) and the results collected which have been obtained by its application to certain members of the ductless glandular group.\*

The present paper deals with a small group of cases (22) in which morbidity of more than one endocrine focus was capable of demonstration—in other words, the so-called pluriglandular syndromes. Readers of the earlier papers of this series will have surmised that the authors do not subscribe to the current orthodox idea of the frequency and significance of the conditions thus designated. The present meager group represents the careful selection from a series of nearly four thousand patients

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\*Rowe and Lawrence (Pituitary) (2); Lawrence and Rowe (Thyroid) (3); Rowe and Lawrence (Gonad) (4).

examined, and are the only ones seemingly in which multi-glandular involvement could be certainly demonstrated. This does not imply that in a large number of endocrine cases evidence of impaired function will not be found in endocrine centers other than that in which the basic condition finds its origin. But these manifestations are purely secondary and as much the result of the general metabolic disturbance as are the concomitant malfunctions of a large group of non-endocrine entities. Further, there can be but little question that primary functional disturbance of rigorously non-endocrine tissues will engender perverted activities of the endocrine group as components of the complete human mechanism. The authors' position may be summarized as a sincere desire to separate cause from effect and to avoid the endowment of sequelae with the authority of a primary causative significance. To illustrate with but one example from the many, it is a frequently recorded fact that serious malfunctions of either the pituitary or the thyroid engender, among many other symptoms, an impairment of the menstrual function. This may become a true amenorrhœa in cases of established gravity. Though the menstrual function presumably has its origin in certain of the cells composing the ovary, and is an external manifestation of an exocrine activity, the popular opinion that regards the control of this function as implicit in the internal secretory activities rests, after all, upon certain assumptions which are not entirely based upon controlled objective facts to support it. Amenorrhœa may exist with seemingly normal ovarian endocrine activity, and patients with severe gonad failure may exhibit normal menstrual function. Castration and transplantation experiments are not germane to the thesis, as all portions of the gland inevitably participate.

The assumption, then, that a pituitary or thyroid amenorrhœa implies a primary participation of the internal secretory activity of the ovary is the result of an elaborate synthesis of unsupported speculations which have, however, been so frequently repeated as to assume with many the authority of established fact. Sight is lost of the fact that with no valid evidence of an interdependence between endo- and exo-crine functions, one rather sweeping assumption becomes vital to the thesis. In this connection, as stated above, we have frequently observed

amenorrhœa with no objective evidence of other than normal ovarian function, and equally, many subjects have been studied demonstrating a definite gonad failure and reporting an entirely normal menstrual history. Only in those anatomical and structural changes in which all portions of the gland participate, do we necessarily find simultaneous inhibition of both internal and external activities. To go but one step further, the existence of amenorrheas of a rigorously non-endocrine origin is generally recognized, as those, let us say, of cardiac or renal origin. If the multiglandular theory be adopted, it becomes necessary to infer a primary gonad failure in these conditions, a conclusion which is not only devoid of any supporting evidence, but against which an impressive array of observed and tested facts can be marshalled. This constitutes a second vital flaw in the chain of speculative reasoning. Without dwelling further on this phase of the topic, it may be said that objective fact imposes straiter limits than does subjective theory.

The advocates of pluriglandular doctrine range from those who see in every phase of endocrine malfunction an algebraic summation of disturbed activity of all the members, established and putative, of the family of ductless glands,\* while others, with a larger measure of conservatism, restrict the concept to those more or less well defined disease pictures which are frequently designated by the names of their proponents.† These represent extremes of thought, and between them is found a protean array of intermediate theories. That the polypharmacy of the manufacturing drug houses has played an important role in confirming an uncritical acceptance of the general concept, must be recognized.§ The scientific warrant for the administration of a complex mixture of glandular extracts is certainly tenuous, and the exhibition of a combination containing ovarian

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\*In the first group (among others, Keith [5], and Beiman [6], should be numbered those writers who courageously discount all cosmic influences and regard ethnic types as determined physically and psychically by intriguing permutations of function in which the whole endocrine family participates. It is unfortunate for the general acceptance of these broad and stimulating generalizations that no objective evidence has as yet been adduced that offends the faintest suspect.

†In this category fall the "multiple ductless glandular sclerosis" of Falta (7), Timme's (8) "thymus adrenal pituitary" compensatory syndrome, and the numerous complexes suggested by the clinical workers of France.

§The *reductio ad absurdum* has recently appeared in a widely circulated device with which by means of a slotted rotating disk any given symptom can be mechanically correlated with the correct pluriglandular preparation designated by number. As a basis for diagnosis and treatment this compares well with a crystal ball or the intricate arrangement of tea leaves.

and mammary substance to the male sufferer conjures up pleasing vistas of speculation.\*

To avoid misunderstanding, a statement in the earlier part of this paper must be reiterated. Many of the existing contradictions and disagreements concerning multiglandular disease rest on the artefactual basis of a question of terminology. The endocrine glands, those at least whose warrant to this designation has been clearly indicated, are among the important regulators of general body metabolism. In the enormously intricate interlocking directorate of the animal mechanism there exist an unguessable number of balanced and delicately adjusted equilibria. The existence of protective compensatory mechanisms forms a necessary corollary to the initial concept and these provide for readjustments to meet the constantly changing conditions inherent in the life processes. With a serious derangement, from whatever cause, such compensations are perhaps not effective, or at the best, only partially so. A pertinent and relatively simple illustration of this point is offered by the regulation of the hydrogen ion concentration of the blood shown in health and disease. Intricate though it be, present knowledge would indicate for it a far greater simplicity than for many other necessary functions which physiology is defining and interpreting. When a disturbed condition arises, many of the functional equilibria are influenced, not in equal measure but in varying degrees. Such changes of level engender others, and in these ramifications of an initial impulse, a vast number of end results will appear in the form of more or less profoundly altered functional levels. Frequently, as we see in any well characterized syndrome, a certain group of common manifestations will be engendered, differing among themselves in degree but not in kind. Contextually, a horde of minor divergences become manifest, portraying the influence of individual difference. As a corollary to this we should equally expect one cer-

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\*Happily many of these preparations are practically inert and their administration allows of all possible psychic benefit without physical injury. Occasionally cases present, however, where this negative benefit does not obtain, and acute conditions have arisen from intemperate use. The greatest single need in the field of glandular therapy today, is the single substance whose physiological activity has been standardized by some dependable biological method of assay. Some progress has been made but much remains to be done. The determination of the iodine content of a thyroid preparation as an index of activity is on a parity with the standardization of digitals by an estimation of the glucose content. Further discussion is unnecessary here since a paper treating this whole question is shortly to appear.



tain end result, of well defined character, to arise from a wide diversity of causes. The same illustrative mechanism already noted will serve to exemplify this point. Acidosis, an end result, is the increase of the hydrogen ion concentration of the blood. The many divergent origins producing this single final product are too well known to require statement. Any given symptom may be a result of any one of a number of wholly dissociated initial causes, and this fact should never be ignored in establishing relationship between effect and cause. Causal elements must be individually evaluated and the final allocation be determined by exclusion.\* With the endocrine glands integral and in some cases essential factors in the body complex, it is obvious that disturbed function in one of them, from whatever cause, will engender resultant disturbances in other members of the group. Equally, however, in the breaking down of normal relationship, a whole series of other foci of control will be subversively affected and their functional levels likewise exhibit change. In this sense, we have pluriglandular disease, but to preserve a just parity, we must apply the same term to those conditions of non-endocrine origin in which the ductless glands participate as secondary and resultant stadia in the progress of the condition. The adoption of such a just and equitable classification would hardly prove constructive in the diagnosis and treatment of disease. Differentiation is the prime requisite, and the larger the measure of specialized function, the greater the opportunity for eliminating, or more usually, partly inhibiting superimposed extraneous influences. Man, rather than the amoeba, is the subject of election for functional study.

Recognizing a mutual interdependence of the ductless glands—in common with all other parts of the mechanism—it is only to that assumption of special esoteric interrelationship as implicit in this single group to which the authors take exception. And the ground upon which this opinion rests is the careful study, by purely objective methods, of individuals in whom a presenting disorder was the result of demonstration and not of inference. If, for example, as a uniform and unvarying result of the removal of the ovaries in adult womanhood and before the menopause, it is observed that the power of assimila-

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\*The present method of differential diagnosis is based on the principle, with the added factor that the endocrine element comes to consideration only after possibly causal non-endocrine disease has been eliminated by test and observation.

tion for galactose is reduced by 50 per cent, one is warranted in assuming that some relationship seemingly exists between carbohydrate metabolism and an influence exercised by the presence or absence of these glands. Such a fact has diagnostic significance when supported by an adequate number of other tested facts. Finally, the authors wish to emphasize that at no time do they deny the possible existence of a true pluriglandular involvement. With the numberless permutations and combinations possible, it would indeed be remarkable if cases did not exist in which a simultaneous primary malfunction was exhibited. In the present series there are a few cases in which such a condition seems to obtain. With such cases, however, as infrequent as they have been found to be, we tentatively suggest that their pluriglandular designation may derive from our own imperfect knowledge rather than from a true multiple involvement. In any case, in our experience, true pluriglandular syndromes, if they exist, are seemingly of the greatest rarity.

It is not necessary to protract this discussion further. Additional supporting evidence for the general thesis constitutes a part of the papers which have already appeared. Further, there is every reason to believe that among many workers in this field the term "pluriglandular" is used in the same restricted sense that here obtains.

Turning to the component members of this series, a necessary preliminary statement is the designation of the individual case with indication of the glands involved. These facts are presented in Table I. (See next page).

Of the 22 cases here listed, 17 owe their plurality to the coexistence of a functional error in one gland with the result of surgical alteration of another endocrine focus. Of these, 14 are complete castrates, while 4 were postoperative cases after thyroidectomy. The seeming arithmetical contradiction, as inspection of the table will show, depends upon one case with surgical intervention in more than one gland. In the light of the previous discussion, the five remaining cases offer a peculiar point of interest. As they will be discussed in detail in the body of the paper, it may be briefly stated that cases B-532 and B-37 are the only ones in which some modifying circumstance does not present. B-18, seen in early middle life as a thyroid fail-

ure, had had a pituitary hyperfunction in prepubertal years with some evidence of a residual posterior lobe overactivity. Her inclusion in the group is partly conventional. S-568 is a frankly doubtful case, the thyroid dysfunction determining her presenting symptoms and the pituitary element resting primarily on the very dubious ground of a seemingly distorted sella. S-686 was a partial castrate and falls between the disease and surgical groups.

TABLE I

GLANDS INVOLVED WITH CHARACTER AND ORIGIN OF DERANGEMENT

Group	Case Number	Function	Pituitary			Thyroid		Ovary	
			Ant *	Post	Origin	Func	Origin	Func	Origin
I—a	B-37	dys.	—	—	Dis	—	Dis		
	b								
	B- 18	dys	—	+	Dis	—	Dis		
	B- 532	dys	—	+	Dis	—	Dis		
	c								
	B- 141	dys	N or —	+	Dis	±	Surg		
	S- 568	dys	N or —	+	Dis	±	Dis		
II—a	B- 659	hypo	—	—	Dis			—	Surg
	S- 741	hypo	—	—	Dis			—	Surg
	S-1327	hypo	—	—	Dis			—	Surg
	S-1343	hypo	—	—	Dis			—	Surg.
	S-1669	hypo	—	—	Dis			—	Surg.
III—a	S- 686	hypo				—	Dis	—	Dis
	B- 109	hypo				—	Dis	—	Surg
	B- 599	hypo				—	Dis	—	Surg
	B- 662	hypo				—	Dis	—	Surg
	B- 976	hypo				—	Dis	—	Surg
	S-1843	hypo				—	Dis.	—	Surg
	b								
	S- 179	dys				±	Surg	—	Dis.
	S- 230	dys				±	Surg	—	Surg
	S- 988	dys				±	Dis	—	Surg
	S-1023	dys				±	Dis	—	Surg
	S-1069	dys				±	Dis	—	Surg.
IV—a	B- 164	dys	?	+	Dis	±	Surg	?—	Surg
									Dis

\*The indicated functional levels of the anterior lobe are tentative and based on probability.

The presentation of our data in tabular form, never entirely satisfactory, is peculiarly hampered in the present instance. With the permutational possibilities on the one hand, and the frequently contrary effects of the several malfunctions on the other, the salient differences shown by the individual cases merge when summated in an average. Some of the cases fortunately present sufficient similarity to make averages typical. In the Pituitary-Thyroid group this helpful condition is lacking. As the individual protocols form a part of this paper, in the inter-

est of economy of space and a just recognition of the intrinsic limitations, we have merged these cases into three sub-groups which are not wholly dissimilar.

In the following discussions, cases will be designated as "hypofunctional" (—) in which all of the observations indicate lowered activities of the glands involved, while "hyperfunction" (+) indicates the antithetical condition. "Dysfunctional" ( $\pm$ ) cases are those where evidence of both phases of activity are seemingly present in a single gland, or where the two glands are at different functional levels. The authors adopt this convention—which is not devoid of sanction—to avoid unproductive and space-consuming dialectic. The definition, at least, permits the reader to visualize the symptom complex.

In the subsequent tabulations, Case B-976 in Group III-a will be omitted. This patient is the only male in the entire series, and his inclusion would only add one more disturbing element to the difficulties of collective presentation.

TABLE II  
PHYSICAL MEASUREMENTS

Group. ....	I			II	III		IV
	a	b <sub>f</sub>	c	a	a	b	a
Glands. . .	Pituitary Thyroid			Pituitary Gonad	Thyroid Gonad		Pituitary Thyroid, Gonad
Function. . . .	—	$\pm$	$\pm$	—	—	$\pm$	$\pm$
Number of Cases	2	2	2	5	5	5	1
Age, Av. (yrs.)	51	36	53	49	42	44	40
Height, Av. (cm)	166	177	171	158	165	160	147
Sitting Height, Av. (cm)	86	92.5	89.5	86	88	87	81.5
Sitting Height, Index	0.518	0.523	0.523	0.544	0.533	0.544	0.554
Chest, Av. (cm)	107	89	87	81	76	79.5	80
Weight, Av. (kgm)	106.2	84.4	70.6	63.1	61.9	67.6	59.8
Area, Av. (sq m)	2.13	2.00	1.87	1.64	1.68	1.70	1.52
Lung Volume, Av. (cc)	1720	3620	2600	2260	2720	2440	2000

Table II contains certain statistics and, incidentally, as measurements are absolute, realizes the worst possibilities of this method of presentation. The dominance of castration as a source of plurality determines the large incidence of cases with gonad involvement. The average ages are higher—well over forty as opposed to the low thirties of the other groups already

described. The greatly lessened incidence of surgical intervention with the endocrine glands in childhood, is probably the determining factor. The average heights are not remarkable, the six feet three inches of B-18 being partly merged in a less conspicuous total. The pituitary cases would seem to have a slight upward tendency, however. Sitting height indices show some variation, the more significant as the whole series is confined to one sex. The single case in Group IV gives a value suggestive of achondroplasia, and those in II-a and III-b are definitely above the normal. Pituitary, reinforced by thyroid, determines an obesity suggested only in one sub-group of the

TABLE III  
"VITAL CAPACITY" MEASUREMENTS

Group.....	I			II	III		IV
	a	b	c	a	a	b	a
Glands.....	Pituitary Thyroid			Pituitary Gonad	Thyroid Gonad		Pituitary Thyroid, Gonad
Function.....	—	±	±	—	—	±	±
Weight—	—	—	±	—	—	—	—
High..... (%)		+24	+14	+52	+31	+36	
Low..... (%)		— 3	+12	— 5	— 4	— 5	
+ Average..... (%)		+24	+13	+21	+31	+14	
Percent of Group.....		50	100	60	20	80	
— Average..... (%)		— 3	—	— 3	— 9	— 5	
Percent of Group.....		50	0	40	80	20	
Net Average..... (%)	+78	+11	+13	+12	— 1	+10	+22
Chest—							
High..... (%)		+23	+16	+22	+20	+30	
Low..... (%)		— 0	+ 7	+ 5	—18	— 4	
+ Average..... (%)		+12	+12	+ 8	+12	+12	
Percent of Group.....		100	100	100	40	60	
— Average..... (%)		—	—	—	—12	— 4	
Percent of Group.....		0	0	0	60	40	
Net Average..... (%)	+43	+12	+12	+ 8	— 3	+ 6	+12
Lung Volume—							
High..... (%)		+ 3	—24	—16	— 2	—14	
Low..... (%)		— 9	—28	—39	—36	—40	
+ Average..... (%)		+ 3	—	—	—	—	
Percent of Group.....		50	0	0	0	0	
— Average..... (%)		— 9	—26	—28	—18	—24	
Percent of Group.....		50	100	100	100	100	
Net Average..... (%)	—48	— 3	—26	—28	—18	—24	—29

Thyroid-Gonad combination. The lung capacities give evidence only of a general influence, and the other data reflect the height and weight relations. As is to be expected, every effort to formulate relative influences in mathematical terms has been

unproductive. Possibly with large groups (fifty or more) presenting closely related functional levels in each combination, statistical analysis might yield a first approximation. Only a later generation will have adequate data. The application of the method of least squares to a few cases is not even a diverting mathematical pastime.

With properly established standards, comparative values enjoy a significance of which the absolute raw data are devoid. Such a comparison, under conditions already described (1), are found in Table III.

The Pituitary obesities are here more strikingly indicated, although curiously enough three castrates with bilobar failure exhibit weights closely in accord with prediction. The small number of cases prevents the observation from being more than interesting. The chest comparisons logically repeat those on weight. All of the groups except I-b show a lowered lung capacity. The pluriglandular group is the lowest of our several series. Seemingly the double burden plays a part.

TABLE IV  
URINE MEASUREMENTS

Group	I			II	III		IV
	a	b	c	a	a	b	a
Glands . . .	Pituitary Thyroid			Pituitary Gonad	Thyroid Gonad		Pituitary Thyroid, Gonad
Function	—	±	± ±	—	—	±	±
Volume Av (cc)	2650	1300	1430	1470	1410	1130	1600
Specific Gravity Av	1 008	1 018	1 022	1 014	1 013	1 017	1 014
Albumin (%)	100	100	0	40	40	60	100
Casts (%)	0	50	0	0	0	0	100
Sugar (%)	0	0	100	0	0	20	0
Salol Av (min)	165	85	60	—	85	—	60
P S P. Elm Av (%)	60	54	56	53	51	59	50

The urine data of Table IV offer a few points of interest.

A depressing effect on urine volume of thyroid and ovary is possibly reflected in the total group averages which are, I—1620 cc., II—1470 cc., and III—1270 cc. Less certainly can be traced a thyroid influence on the appearance of albuminuria, the relative percentages being, I—60, III—50, and II—40. A

posterior lobe failure apparently compensates for the glycosuric effect of castration in Group II no more than does the hypoactive thyroid in Group III-a. The indications of the phthalein test are not remarkable.

The Nitrogen Partition values (Table V) might be interpreted as indicating an increased influence of the Gonad over Pituitary and Thyroid in the production of a high Residual fraction. Comparison with the data from the series of uni-

TABLE V  
NITROGEN PARTITION

Group.....	I			II	III		IV
	a	b	c	a	a	b	a
Glands.....	Pituitary Thyroid			Pituitary Gonad	Thyroid Gonad		Pituitary Thyroid, Gonad
	—	±	±	—	—	±	±
Total Nitrogen, Av.(gms.)	12 17	9 20	9 84	9 17	7 03	10 02	9 71
Urea Nitrogen...Av. (%)	81.1	80 5	76 7	78 6	80 4	80 6	83 7
Uric Acid Nitrogen Av. (%)	2 4	2 5	4 6	2 1	2 1	2 1	1 5
Ammonia Nitrogen Av. (%)	4 6	6 2	2 0	4 3	4 8	4 2	3 6
Creatinin Nitrogen Av. (%)	4 4	5 4	4 5	4 6	4 8	3 8	3 1
Residual Nitrogen Av. (%)	7 5	5 4	12 2	10 4	7 9	9 3	2 1
% = or above 9%.....	0	0	100	60	20	60	0

glandular involvements in the preceding papers shows this not to be the case, however. The values here signify no more than that the metabolic error reflected in a high residual nitrogen is shown by all of the endocrines—and other studies betray a similar result in a fairly large group of non-endocrine diseases.

The chemistry of the blood, as presented in averages (Table VI), offers but little information. The relative uric acid increase, which is characteristic of uncomplicated pituitary malfunctions, is here not strikingly present (30 per cent in pituitary as against 20 per cent in non-pituitary cases). We record the fact without offering explanation. Residual nitrogen values assume significant heights only in the single case of Group IV. That this latter should exhibit it is not surprising in the light

of her chronic interstitial nephritis and diverse endocrine pathology. The blood sugar sequence is not remarkable, the lower value in the Hypo-Thyroid-Gonad group being probably fortuitous.

TABLE VI  
BLOOD CHEMISTRY

Group. . . . .	I			II	III		IV
	a	b	c	a	a	b	a
Glands. . . . .	Pituitary Thyroid			Pituitary Gonad	Thyroid Gonad		Pituitary Thyroid, Gonad
Function. . . . .	—	—	±	—	—	±	—
Non-Protein Nitrogen Av. (mgm)	38	30	31	32	33	34	44
Urea Nitrogen Av. (mgm)	19	16	16	15	16	17	21
Uric Acid Av. (mgm)	5.0	3.2	3.4	3.6	3.6	4.0	6.0
Net* % = or above 4 mgm. . . . .	0	50	0	20	20	20	0
Creatinin Av. (mgm)	1.9	1.4	1.4	1.5	1.5	1.5	1.4
Residual Nitrogen Av. (mgm)	16.7	12.3	13.3	15.2	15.2	15.1	20.5
Sugar. . . . . (mgm)	127 <sup>‡</sup>	97	99	98	87	103	97

\*All cases demonstrating nephritis have been deleted.

<sup>‡</sup>Value too high. Patient was very obese and blood obtained with difficulty.

In the Blood Morphology (Table VII), two or three apparent relationships present. The tendency toward a secondary anaemia of Groups II and III, and the higher level of the lymphocytosis in Group III, are probably apparent rather than real. The association of an eosinophilia with the pituitary cases harmonizes with the observations with the uncomplicated cases. No record of serological findings is tabulated, as the response to the several tests was uniformly negative.

With the data of the Respiratory Metabolism (Table VIII), we find almost for the first time clear evidences of the summation effects of the several glands. This is probably due to the fact that again we are dealing with relative values, and the several magnitudes assume a concrete significance through the use of a standard of comparison allowing for individual variation. With the thyroid recognized as the primary regulator of



the basal rate—at least in the group under consideration—with the pituitary and gonad on a basis of approximate parity—the pituitary perhaps slightly more effective—we should expect to find real differences. Pituitary and Thyroid failure together determine the lowest level, and while the dominance of the Thyroid is again manifest in the Thyroid-Gonad failures, Pituitary and Gonad together cannot lower rates to the depth which participation of the Thyroid connotes. Equally, antagonistic levels

TABLE VII  
BLOOD MORPHOLOGY

Group	I			II	III		IV
	a	b	c	a	a	b	a
Glands	Pituitary Thyroid			Pituitary Gonad	Thyroid Gonad		Pituitary Thyroid, Gonad
Function	—	±	±	—	—	±	±
Haemoglobin Av (%)	100	90	88	86	89	83	100
Color Index	0 76	0 94	0 84	0 88		0 90	0 90
Erythrocytes Av (10 <sup>6</sup> )	6 56	4 80	5 22	4 87	4 77	4 59	5 56
Leucocytes Av (10 <sup>3</sup> )	10 0	7 4	5 6	8 9	8 2	8 2	7 9
P M N Neutrophiles Av (%)	60	56	54	57	55	46	57
% = or above 75%	0	0	0	20	0	0	0
Lymphocytes Av (%)	34	35	39	35	36	49	37
% = or above 33%	100	50	100	60	60	100	100
Eosinophiles Av (%)	1	2	2	4	2	1	1
Net* % = or above 3%	0	50	50	10	20	0	0
Monocytes Av (%)	5	6	5	4	7	4	5

\*All cases demonstrating a non-endocrine cause of eosinophilia have been deleted

are strikingly shown in the several dysfunctional groups. The single case in Group IV probably shows a residual hyperactivity of the thyroid which compensates the depressing effect of the conjoint gonad and anterior lobe failures. Blood Pressures and Pulse Rates show similar tendencies but without the clarity of definition of the Basal Rate measurements. As noted in the table, a single hypertensive case in any one of these very brief series influences the group average unduly. The effect of the Gonads on Alveolar Carbon Dioxide is not strikingly exhibited in the presence of either the Pituitary or of the Thyroid.

As with the Respiratory Metabolism, the additive character of the carbohydrate influences gives a true significance to certain of the collective averages. For the sake of clarity, the

reader may be reminded that the level of tolerance for galactose for the normal adult female is at forty grams. Castration or severe functional failure of the gonads lower this to twenty grams, less severe to thirty, the stadia being determined by the conditions of applying the test and not implying abrupt transitions. The posterior lobe of the pituitary may condition, by overactivity, a complete extinction of the tolerance, or equally, by a lowered function may raise it 200 per cent or more. With the thyroid, the sense of the change follows the pituitary, but the magnitude varies widely and significantly. Over two-thirds of the thyroid cases show a normal tolerance (for galactose), and the remainder exhibit changes of the order of  $\pm 33$  per cent. Finally, in the normal sex cycle immaturity connotes the

TABLE VIII  
RESPIRATORY METABOLISM

Group.....	I			II	III		IV
	a	b	c	a	a	b	a
Glands.....	Pituitary Thyroid			Pituitary Gonad	Thyroid Gonad		Pituitary Thyroid, Gonad
Function.....	—	±	±	—	—	±	±
Basal Metabolism	—	—	±	—	—	—	—
Deviation—High... (C%)	—	—22	—3	—7 <sup>†</sup>	—21	—6	—
Low.... (C%)	—	—11	—25	—23	—30	—14	—
Average..... (C%)	—34	—33	—14	—20	—26	—11	—1
Blood Pressure							
Systolic... Av. (mm)	128	106	161*	106	117*	104	165
Diastolic... Av. (mm)	80	71	81*	66	72*	72	110
Pulse Rate Av. (per min)	72	56	80	64	61	81	84
Respiration Rate							
Av. (per min)	20	12	11	14	15	13	16
Temperature... (deg. F)	97.8	98.2	97.7	97.7	97.1	98.6	98.0
Alveolar CO <sub>2</sub> Av. (mm.)	46	43	37	41	39	42	33
% less than 35 mm....	0	0	50	0	0	20	100

†Value too high. Patient was nervous. Omitted in deriving average.

\*A single case of hypertension influences the average unduly.

same level as that of castration, while the menopause may produce no change or more usually a depression to thirty grams. The data derived from the application of this test are given in some detail in Table IX.

A closer analysis of the sub-groups is most informative. In the first (I-a), a single case, pituitary underactivity raises the tolerance 100 per cent. In the second (I-b), the depressing influ-

ence of the posterior lobe outweighs the upward thyroid tendency, and the result is a depression of moderate degree. In the dysfunctional Pituitary-Thyroid section (I-c), the Thyroid inhibition of the Pituitary depression is lessened, and the low level of —83 per cent is realized. In Group II, castration has lowered the tolerance to twenty grams, and the more powerful augmenting power of posterior lobe failure on assimilation capacity raises the tolerance over 100 per cent above prediction.

TABLE IX  
GALACTOSE TOLERANCE

Group	Case Number	Function			Galactose Tolerance			Group Average
		P (post.)	T	G	Normal	Observed	Deviation	
I—a	B- 37	—	—		30	60	+100	+100
	b							
	B- 18	+	—		40	30	— 25	— 38
	B- 532	+	—		10	20	— 50	
c	B- 111	+	±		30	5	— 83	— 83
	S- 568	+	±		30	glycosuria	?	
II—a	B- 659	—		—	20	60	+200	+110
	S- 744	—		—	20	30	+ 50	
	S-1327	—		—	20	40	+100	
	S-1313	—		—	20	40	+100	
	S-1669	—		—	20	40	+100	
*III—a	S- 686		—	—	40	30	— 25	+ 13
	B- 109		—	—	20	20	± 0	
	B- 599		—	—	20	30	+ 50	
	B- 662		—	—	20	30	+ 50	
	B- 976		—	—	30	30	± 0	
	S-1843		—	—	20	20	± 0	
b	S- 179		±	—	40	10	— 75	— 19
	S- 230		±	—	20	glycosuria	?	
	S- 988		±	—	20	10	— 50	
	S-1023		±	—	20	20	± 0	
	S-1069		±	—	20	30	+ 50#	
IV—a	B- 164	+?	±	—	40	10	— 75	

\*Note inclusion of Case B-976.

#Marked Thyroid failure under heavy medication at time of test and included in dysfunctional group for this reason

Unweighted Averages		
P + T	Hypo-	Dys-
P + G	+100	—60
T + G	+110	—
P + T + G	+ 13	—19
	—	—75

Turning to Group III—Thyroid and Gonad—the first case in sub-group “a” is a possible functional ovarian failure superimposed on a hypofunctional thyroid. This determines a slight lowering from the normal level. The second and sixth cases

were castrates with a functional hypothyroidism that did not affect the tolerance, while in the third and fourth the magnitude of the thyroid depression raised the tolerance 10 grams above the level determined by the castration. The fifth case, the only male in the entire series, shows a normal tolerance, the thyroid failure not being sufficient to raise the assimilation limit, and the castration being devoid of influence on this function. The divergent tendencies are more variably expressed in the individual members of Group III-b, which is not entirely uniform in its composition. For example, in Case S-179, a functional gonad failure and thyroid dysfunction (surgical), the one influence supplements the other and produces a level 75 per cent below prediction. On the other hand, Case S-1069 by castration has a predicted level of twenty grams, but the superimposed thyroid failure raises the assimilation limit to thirty, or an increase of 50 per cent. This latter subject was under drastic thyroid medication and in spite of this the basal rate was still —12 per cent. As was discussed at some length in the thyroid paper, we have some reason to believe that this gland produces more than one active principle, and that while the energy regulating hormone—thyroxin or something similar—may be supplied in exact measure, another agent which influences the carbohydrate tolerance may be simultaneously either in excess, equal amount or deficit. The other tolerances observed in the group are those which could be predicted from the algebraic sum of the several agencies operative.

This concludes the presentation and discussion of the more salient points elicited by the laboratory examination. Many other observations were made with each patient but their nature precludes presentation in summarized tabular form.

To conclude this discussion, a few of the characteristic influences are sufficiently salient to manifest themselves even under the inhibiting conditions of tabular presentation. These are, in the main, the relative values resulting from comparison with standards absorbing individual variation or, as in the case of the galatose tolerance, where additive relations exist. The results of the special clinical observations of the Consulting Staff adapt themselves even less well than do the laboratory data to the tabular form of presentation.

The characteristic features of disturbance of the individual glands has already been adequately covered in the previous papers. While the protocols of each case will be given later in the paper, a few of the clinical data may, for the sake of convenience, be collated for discussion. In the main, such analysis is unprofitable, as the factors of variation are too many to make collective consideration significant. The exceptions will be dealt with in the next section.

## PART II

Note has already been made of the relatively greater age of this group at the time of first admission to the Clinic. Likewise, the age of onset of the chief complaint, as given, falls in a later decade than was the case with the uncomplicated endocrinopathies. The significant data are collected in Table X.

TABLE X.

AGE		
Decade	Age of Admission	Onset
11-20 years.....	1	2
21-30 years.....	0	5
31-40 years.....	6	7
41-50 years.....	8	5
51-60 years.....	5	2
61-70 years.....	1	0

The first is a dependable datum, but the second is largely influenced by subjective factors that cannot be evaluated.

The average duration of the chief complaint in the group is ten years, a value, as will be shown in a later table (XIII), exceeding the dates of the thyroidectomies but falling short of those of the castrations. The chief complaints are varied and in most of the cases more than one is presented.

Fatigue in this group, as in those of the uncomplicated endocrinopathies, is a major symptom. Half presented it as a chief complaint, and practically all of the remainder mentioned it as a secondary disability.

Pain appeared as a major ailment in one-third, and as a contributory factor in practically all of the remaining cases. It

was rarely confined to a single area. The frequent incidence of pain as a symptom has already been noted in the Gonad paper, and it must be remembered that two-thirds of this group had been castrated.

TABLE XI  
CHIEF COMPLAINTS

Fatigue .....	11
Pain .....	7
Obesity .....	4
Headache .....	4
"Nervousness" .....	4
Dyspnoea .....	3
Anaesthesias } .....	3
Paraesthesias }	
Skin Eruptions .....	3
Deafness .....	2
Digestive Disorders .....	2

Four patients complained of obesity and two more exhibited it in a marked degree. In view of the usual association of obesity with endocrine failure, an analysis of this group is interesting.

TABLE XII.

OBESITY

Group	Obese > +15%	Normal +15% to -10%	Thin < -10%
Pituitary-Thyroid .....	2	3	0
Pituitary-Gonad .....	1	4	0
Thyroid-Gonad .....	3	5	2
	—	—	—
Total .....	6	12	2

Case B-164 has been omitted.

While the normal limits adopted are perhaps too liberal, of this group three were above, three equalled, and six were below prediction, a fact offering further emphasis on the unwisdom of assuming that endocrine failure necessarily determines overweight. The dysfunctional thyroid case might be assumed to

produce emaciation, but two of the six obese patients, a just proportion, fall in this group. Headache, unassociated with menstruation and "nervousness" were or had been common complaints. The frequency of this first symptom in the endocrinopathies has recently been stressed by Drury (9). The other complaints as offered are generally recognized as frequently associated with endocrine disease.

Four of the patients gave a family history of endocrine disorders, diabetes and thyroid disease being mentioned.

In their own histories a principal point of interest lies in the surgical events which had determined the pluriglandularity of so large a portion of the group.

TABLE XIII.

Operation	No.	Date (Average)
Thyroidectomy .....	4	6 years previously
Single Oöphorectomy .....	2	7 years previously
Double Oöphorectomy ....	14	12 years previously

Of the thyroid subjects, two had had more than one operation, while several of the castrates had had one ovary removed prior to a second and complete operation.

The thyroid status of the group at the time of admission showed four operated cases as noted above, fourteen with no evidence of thyroid enlargement, and three with small goiters, one in each of the three major groups.

TABLE XIV-a.

MENSTRUAL HISTORY

Year	(a) Onset	Number
10 years.....		1
11 years.....		3
12 years.....		4
13 years.....		5
14 years.....		4
15 years.....		2
16 years.....		1
17 years.....		1

With so general an involvement of the organs of generation, the facts of the sexual histories are very informing. Almost all of the group had passed a menopause, artificial or natural, but the previous menstrual histories can be collected for presentation.

The relative values here would compare with those of any other group selected at random. Two-thirds fall within the conventional span of 12-14 years, and but three show a really early or delayed onset. No racial influence could be traced in these latter as they were all of English birth or origin.

TABLE XIV-b.

(b) *Character*

Rhythm		Flow		
		Increased	Normal	Diminished
Irregular 8	Increased .....	0	2	0
	Diminished .....	2	1	0
	Both .....	1	2	0
		—	—	—
	Total .....	3	5	0
Regular 13	.....	1	11	1
Grand Total.....		4	16	1

Normality of function seems to be the rule with eleven patients both regular in rhythm and normal in amount, while two more are normal in rhythm and five more in amount. Three show the conventional irregularity of thyroid disease, the others scatter with but one showing a diminished flow. This is somewhat striking in view of the large number subsequently operated upon. Apparently, cystic degeneration—a common cause for castration in this group—does not lessen the flow with the same frequency that it causes irregularity.

The reproductive power of the group is a natural sequel to the preceding.

One woman is omitted as she was married twice, conceived at least thirteen times, bore two children and had at least eleven induced abortions. The second child was delivered by Caesarian section and at this time a pan-hysterectomy was performed.

The figures given above are extremely interesting in view



of the endocrine status of the group. All of them were endocrine cases although not all were certainly pluriglandular. In a larger group (100) drawn from the gonad series, 31 per cent were sterile and 10 per cent had conceived, only to miscarry;

TABLE XV.

FERTILITY

Unmarried .....	5
Castrated before marriage.....	2
	—
Total .....	7
Sterile .....	2
Productive .....	12
	—
Total .....	14
Of 11 married women:	
Children .....	18
Miscarriages .....	8
Abortions (induced) .....	1
Tubal Pregnancies .....	2
	—
Total Conceptions .....	29

in other words, 59 per cent only had been productive. In this group 86 per cent of the women capable of bearing children had done so, the 14 per cent sterile comparing well with the average (10-12 per cent) given by Reynolds and Macomber (10) as a fair value for unselected groups.

An inference here would be that the endocrine condition was established in most of the cases in adult years after maturation and opportunity for exercise of a normal procreative function. The previous histories and ages of onset, as given, would support this idea. Of the five subjects without surgical complication, two were unmarried, one had borne five children with one miscarriage, one had conceived but terminated the pregnancy voluntarily, and the third was a young girl, 19 years of age, who had had one miscarriage in her year of married life.

While one must be conservative in the interpretation of end results in a series of cases presenting such numerous evi-

dences of conjugate endocrine involvement, the foregoing analysis certainly does not offer a direct support to the theories of pluriglandular involvement in childhood so frequently adduced to explain developmental aberration.

One other minor point may be touched upon. In the earlier papers emphasis has been laid on the frequent incidence of tonsil involvement. In the present group six had been operated once or more, four had diseased tonsils, while eleven were normal as regards the tonsils. The percentage of positive cases here falls somewhat behind the other groups but is still at a significant level.

As was noted earlier in the paper, the very nature of the cases composing this group seriously inhibits collective presentation. We have felt it better, in the interest of our readers, to conclude the discussion with a brief protocol of the case of each of the patients here included. The limitation of space determines brevity but effort has been made to include the salient details.

### PART III

#### CASE PROTOCOLS

##### GROUP I-a. PITUITARY FAILURE AND THYROID FAILURE.

CASE B-37. This patient was first seen in January, 1923. She gave as her chief complaint, excessive somnolence. She had had an attack of influenza at the time of the epidemic and her seizures of "uncontrollable sleep" began shortly afterward. There was no warning of the seizure but in the midst of sewing, reading or even talking the eyes closed and to outward appearances she would lose consciousness. She maintained that she was conscious of what went on about her during these attacks. The attack usually lasted from 10 to 15 minutes, they showed no periodicity and they occurred at intervals varying from days to weeks. The patient was also extremely obese but did not offer this as a complaint. Her previous hospital examination elsewhere had led to a diagnosis of pituitary failure but the patient had not benefited from a brief course of treatment which had been subsequently given. The family history gave heart failure as the cause of the father's death. There were six living siblings of whom one, was a surgical castrate who had also been studied by us. Cancer was recorded in the earlier generations. The patient had had measles and chicken-pox in childhood and typhoid at the age of 34. She had had attacks of arthritis at different times during her adult life. She reported headaches only at the time of her periods and a negative gastro-intestinal and genitourinary history. Of late years she had had some dyspnoea with palpitation and also reported occasional swelling of the feet and ankles. She had matured at 13 and believed her periods to be fairly regular. At the age of 51 the menstrual function was apparently unimpaired and she had a 4-day

period shortly before entering the hospital. Her highest weight she believed to be about 250 pounds. She weighed about 240 pounds at the time of entrance. The patient was a heavy coffee drinker, when at home averaging nine or ten cups a day. The physical examination showed a well-developed but very obese woman in middle life, her obesity tending toward a girdle distribution. The head was covered with a moderate growth of coarse dark hair; elsewhere there was no excessive pilosity. The teeth were small and irregularly spaced. There was a roll of fat around the neck and no enlargement of the thyroid could be demonstrated. The breasts were very large and pendulous, the lungs and the heart, apparently normal. The abdomen was very obese which prevented an entirely satisfactory examination. There were numerous varicose veins on the lower extremities and a small tumor growth in the lateral aspect of the right knee just outside of the patella. The knee jerks were somewhat sluggish but equal. The urine examination showed a volume of over 2½ liters; the elimination was poor, balance fair. Albumin was reported but no other abnormalities. The sediment was normal. The protein intake as gauged by the nitrogen elimination was ample and the partition formula of the latter within normal limits. The blood showed a high haemoglobin and red count, a marked lymphocytosis (60 per cent) and was otherwise normal. Chemically the blood showed an absolutely high uric acid and a slightly high blood sugar, the latter probably due to an emotional response as the venipuncture was difficult and painful. The alveolar carbon dioxide was a high normal. The serological tests were negative. The sugar tolerance was increased 50 per cent above prediction, a dose of 60 grams of galactose being necessary to produce a positive response in the urine. The patient was 81 per cent above her predicted weight, while the lung capacity was less than half that predicted by the Dreyer standard. The basal rate was —34 per cent, the pulse and temperature being substantially normal, the blood pressure relatively somewhat low. A neurological examination gave substantially normal findings. It gave no evidence of organic lesion. The patient was somewhat dull mentally without exhibiting any psychotic element of significance. The eye examination showed normal fields, blind spots slightly enlarged and apparently normal discs. A radiogram of the aortic arch showed a thickened wall. The remaining chest X-ray findings were normal as were those of the skull, sella and sinuses.

*Discussion:* The picture presented by this patient was clearly endocrine but the actual gland or glands at fault were not easy of determination. The large volume of the urine, the high blood uric acid, normal nitrogen partition, the somewhat low blood pressure, normal pulse rate, 'phthalein test, and relatively large increase in the tolerance threshold were all suggestive of pituitary deficiency. In addition, the type of distribution of her obesity, the history of her presenting difficulty, and a number of other points elicited in the physical examination and history were confirmatory. On the other hand, the magnitude of the deviation of the basal rate was greater than we have ever associated with uncomplicated pituitary failure. The lack of excessive hair growth and other points of a like nature, tended to emphasize the thyroid element. At the time of the examination it was felt that this case might properly be classed as a true pluriglandular condition with lowered functional activity both of the pituitary and the thyroid. That a therapeutic test might be given, the patient was placed on thyroid medication alone with observations made at fairly frequent intervals. The basal rate improved somewhat, reaching in mid-June a level of —19 per cent. The

weight was unchanged, the pulse remained in the mid-seventies, and there was no effect on the sugar tolerance. The thyroid dosage at this time was somewhat variable as the patient's cooperation was not complete. Her average intake, however, was of the order of 5 or 6 grains per day. Pituitary medication was added to her variable thyroid intake and in October of the same year (1923) a partial study was made. The urine volume had dropped somewhat but was still ample, averaging about 1800 c.c. Albumin persisted. The earlier normal residual nitrogen remained unchanged. The earlier lymphocytosis was at the same high level. Body weight had decreased but three kgm., and practically all of the other findings were at the earlier level. Two changes, however, were recorded. The basal rate had become normal and the sugar tolerance had dropped to 50 grams. The patient was discharged with the recommendation to continue both the thyroid and the pituitary treatment and was seen again in March of 1924. There was reason to believe that again she had not been consistent in following her treatment but equally that she had taken a good deal both of thyroid and of pituitary substances. The urine presented the same general picture as did the blood chemistry and blood morphology. The patient had lost some 10 kilograms more but was still markedly obese. The basal rate at the time of the study was —12 per cent with a pulse of 70. The "sugar tolerance" could not be secured.

This patient represents one of the few cases in our very long series in which, seemingly, there was simultaneous primary involvement of two endocrine glands. On thyroid medication alone the patient showed but little change, while her history showed that her earlier pituitary medication had been equally ineffective. The combination of the two was apparently necessary to normalize the basal rate and induce such changes as were recorded. Her attacks of drowsiness had become less during the fifteen months but as they had been showing a lengthening interval before we studied the case, it is not legitimate to ascribe this improvement certainly to the medication. The patient's relatively slight loss of weight was undoubtedly ascribable to her unwillingness to curb her large appetite. She was studied early in the present series of investigations. Certain laboratory procedures which have since become available and, more importantly, a number of skilled opinions in the specialized fields of medicine were not available at the time of this study. Shortly after the last observation in 1924 the patient moved to the far West and we have had no further news of her since that time. From the data available, recognizing its incompleteness, we feel constrained to report this patient as presenting a genuine pluriglandular condition.

#### GROUP I-b. PITUITARY DYSFUNCTION WITH THYROID FAILURE.

CASE B-18. This patient was admitted in 1922 for a study of her endocrine status. She was a woman of 35, nearly 6 feet 3 inches tall, who complained of an anaesthesia of the middle third of the body accompanied by incontinence of bladder and rectum. Three years previously she had been admitted for retention of urine and the use of the cystoscope revealed her anaesthesia in this region. Under treatment the condition cleared up in about 3½ months. When readmitted in 1922 for this study, she stated that she had been unconscious of the passage of feces since her illness three years before, and that a similar condition existed in regard to urination. It seemed probable that some degree of the anaesthesia of the anterior

portions was of much longer duration, since she had never been conscious of the menstrual flow escaping from the vagina. There had never been any sex urge.

A second complaint was recorded, namely, back pain, from which she had suffered for about 10 years although she gave a history of weak back from the age of 10. She had been under orthopedic care and had worn various supporting appliances, from which she derived some benefit, for a number of years.

PLATE I



CASE B-18

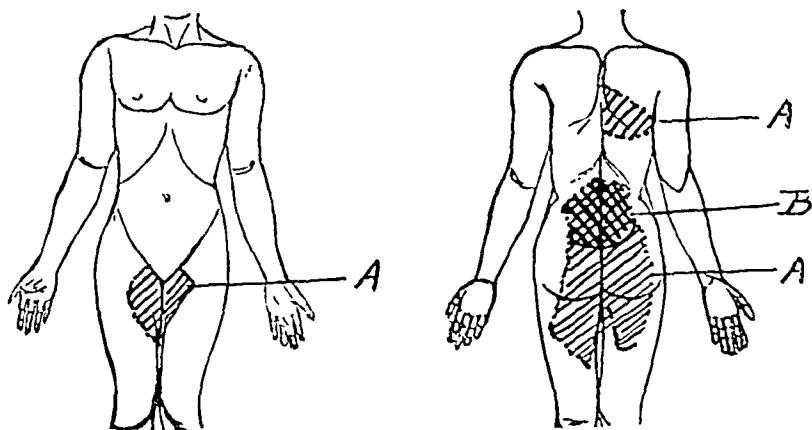
Both parents had died of diabetes and both were extremely obese, the father weighing 300 pounds and the mother 275 pounds. Her only sibling, a brother, had been 6 feet 4 inches tall and had recently died of advanced nephritis. The patient's own history included minor ailments and scarlet fever previous to her eighth year, at which time she had a severe attack of chorea, following which she had had to learn to walk again. Between the ages of 10 and 12 she grew to her present stature. The menses had been established at 13, and showed a somewhat shortened regular interval and scanty flow. The mental development had been wholly normal. The physical examination showed a very tall girl with low sitting height index

(0.50) and a tendency to girdle obesity not shown in other parts of the body which were somewhat underweight (see Plate). The head and body hair was somewhat scanty and of normal distribution. The thyroid was somewhat enlarged, the chest and abdomen normal. Rectal and vaginal findings were normal except for the anaesthesia. An earlier radiogram of the spine had shown no spina bifida; a very complete series of plates of the entire body showed no pathological changes in either the bony structure or the viscera. The neurological findings will be discussed in detail elsewhere. Summarized: three years previously, the tendon reflexes had been reported as normal; at the time of this examination the Achilles and knee jerks were absent. The anaesthetic areas are shown in the accompanying chart (q. v.).

The urine volumes were normal, elimination and balance good. Albumin was present; the remaining findings, including the nitrogen partition, were normal. The blood morphology was normal, the blood chemistry equally so, and the serological tests were negative. The 'phthalein elimination and  $\text{CO}_2$  level were normal. The sugar tolerance was slightly depressed, the "vital capacity" comparisons substantially normal. (The low sitting height index has already been noted.) A series of basal rate determinations gave values between  $-20$  per cent and  $-25$  per cent with definitely low blood pressure and slow pulse. A urica curve was normal.

*Discussion:* With the patient's bodily habitus and history, the first thought here would be of an earlier over-active pituitary pass-

PLATE II



CASE B-18

ing through a functional involution state and presenting the common dysfunctional formula. The sugar tolerance would harmonize with this idea, as would the observed level of the basal rate. The eosinophilia and high blood uric acid are lacking, and the blood pressure, pulse rate and alveolar  $\text{CO}_2$  are at levels more suggestive of thyroid failure. The observed basal rates were as low as  $-25$  per cent, a somewhat extreme value for anterior lobe failure—and it was questionable if the patient were ever in a truly basal condition. The thyroid enlargement was not necessarily meaningful as it is a not infrequent report in cases of uncomplicated pituitary disease, to say nothing of its frequency in normal and non-endocrine conditions. In other words, there were evidences of a possible true pluriglandular

state in which the pituitary was the earlier and recessive, and the thyroid failure, the later and dominant element. On this basis a tentative diagnosis was offered and thyroid medication instituted. The anaesthesia gradually cleared up and the incontinence disappeared. This response to the thyroid medication is felt to offer some support to the initial diagnosis. The later history of this subject will be reported later; none of its events have thrown any more light on the basic, underlying endocrinopathy. In fairness, we feel that it must be reported as a pluriglandular involvement, although the pituitary element was principally represented by structural residua.

CASE B-532. The patient was a woman of 33 referred to this Clinic primarily for obesity. She had been married for 10 years during which time she has six pregnancies, the first resulting in a miscarriage at three months and the other five in viable children three of whom, however, showed a definite retardation in mental development. At the time of her marriage the patient was not strikingly obese. After this event, however, she began to increase weight, and after the completion of her fourth pregnancy she weighed 160 pounds. She then began to gain more rapidly and in the course of 5 years reached nearly 250 pounds. By rigorous dieting she reduced herself about 40 pounds in the course of a year, but prior to admission had begun to gain again and weighed 215 pounds when we first saw her. Both of her parents were said to be extremely nervous. She had two brothers who were well and apparently normal. She reported one aunt who was a diabetic and extremely obese. Of her own history she reported the usual minor ailments of childhood together with scarlet fever, influenza at the time of the epidemic, and pneumonia in 1922. A breast abscess was lanced in 1917. She had occasional headaches when fatigued and what she described as neuralgic headaches when her teeth were in poor condition. This latter condition was seemingly one of recurrence and there was a long history of dental troubles. She complained of vertigo during her pregnancies. Within the past three years there has been much thinning of the hair on the vertex. She noted optic fatigue, some loss of hearing, frequent severe attacks of rhinitis and, she believed, some nasal obstruction. The cardiac history was substantially normal. She had been fatigable for a number of years and this condition was accentuated during her pregnancies. After each confinement there was a brief period when the patient had night sweats. Experience had shown that unless food were taken shortly after arising there was a tendency to nausea. The periods began at 13, were regular, and apparently normal in amount. She had had recurrent attacks of pimples on the breasts. For many years she had had some intermittent pain in the legs and knees. There was also stiffness of the neck, and at the time of the breast abscess there was "articular rheumatism" in all the joints. Of later years she had experienced numbness and cramps in the legs and tingling in the hands associated with coldness of all extremities. There had never been any evidence of mental impairment, she having made excellent records at school and college. The physical examination showed a definitely obese woman with a marked tendency toward girdle distribution. The eyes and ears were normal, the tonsils slightly enlarged and cryptic, teeth in poor condition, no apparent thyroid enlargement, heart and lungs normal, abdomen markedly obese, arms and legs large, ankles possibly slightly edematous; the hands, wrists and feet were small. There was a slight scoliosis, a slight cervical adenopathy; the skin was somewhat hypertrophic and dry. Routine neurological findings were normal. The urine was normal in amount;

elimination and balance were poor. One specimen showed albumin and all, a trace of sugar; the sediments were normal. The nitrogen partition determination showed an elimination indicating a somewhat low protein intake; the partition formula was normal. The blood showed a marked relative lymphocytosis (47 per cent) and a  $3\frac{1}{2}$  eosinophilia. The blood uric acid was above the normal level, the blood sugar normal. The serological findings were normal. The 'phthalein elimination was somewhat low. The patient's sugar tolerance was half the level normal for a woman of her age and sexual status. By the Dreyer standard she was 38 per cent overweight, but her obesity was actually in excess of this as the sitting height index was 0.55, a value well above the normal. Her lung capacity was slightly above prediction. Two independent basal rate measurements gave a value of 44 per cent below prediction, with slow pulse and a blood pressure just below 100. Her alveolar  $\text{CO}_2$  was normal. X-ray findings of the heart, lungs and mediastinum were all normal; of the teeth showed much alveolar absorption and several periapical abscesses. A neurological examination gave no positive neurological findings. A nose and throat examination demonstrated a slight septum deviation not sufficiently important to warrant interference. A cardiogram showed a slight sinus arrhythmia and low voltage but was otherwise normal; this finding was confirmed by a heart consultation. The eye grounds showed yellowish discs, enlarged blind spots, and some symmetrical contraction of the form and color fields.

*Discussion:* The majority of the findings in this case were entirely harmonious with the general picture presented by a case of pituitary dysfunction. The normal urine volume, slight glycosuria, the normal nitrogen partition formula, the slight eosinophilia, high blood uric acid, lowered galactose tolerance, normal lung capacity, high alveolar carbon dioxide, integrate to form a picture of pituitary disease. This conclusion is supported by a number of points in the history and physical examination. On the other hand, the basal rate was at a level which had been observed by us only in thyroid failure; with this was a blood pressure definitely lower than that usually recorded in pituitary disease, and also a slow pulse. A urea curve showed a normal shape with somewhat depressed elimination, and the 'phthalein test was somewhat low—factors again more suggestive of thyroid failure. Here again the various data, while defining unmistakably an endocrine disturbance, exhibit magnitudes and directional relationships which it would be difficult to associate with the uncomplicated failure of a single gland. The patient was put on thyroid medication. Four months later she had lost less than 2 kilograms, exhibited an unchanged blood pressure and pulse rate, and a basal rate still 27 per cent below prediction. Thyroid medication alone was continued for three more months without producing any change, the patient gaining 0.2 kgm. in weight and showing a basal rate of —23 per cent. Pituitary medication was then added to the thyroid and later reports show a definite improvement, although we have no laboratory records of later basal rate measurements.

This case like that of B-37 is seemingly one of simultaneous involvement of both pituitary and thyroid. The pituitary formula is not the same, as in this case the posterior lobe exhibits a definite over-activity, while in the first a bilobar failure was the condition. With the data available and such knowledge as we possess of endocrine disease at this time, diagnosis of a pluriglandular condition involv-



ing both the thyroid and the pituitary is seemingly the only one which is warranted.

GROUP I-c. PITUITARY DYSFUNCTION WITH THYROID DYSFUNCTION.

CASE B-141. The patient's chief complaint was of a steady increase in weight coupled with an increasing dryness of the skin and an intermittent flushing of the chin, cheeks and upper chest. Some 17 years previously the patient began to develop a disturbing nervousness and to lose weight. This condition continued progressively until 1911 when a diagnosis of hyperthyroidism was made and an operation performed. Two years later there was some recurrence of the earlier symptoms and on her own initiative the patient instituted a course of thyroid medication. Somewhat later this procedure was approved by her physician. The thyroid therapy was subsequently discontinued and a year before the patient was admitted to this Clinic she began to develop the symptoms which ultimately led to her reference here. She was a woman well above the average height; one of her siblings was 6 feet 4 inches tall at the age of 14 and was mentally deficient. The father had diabetes for a long time prior to his death; the mother had had Graves' disease, was operated upon and developed myxedema before her death from heart failure. Eight siblings were alive and well. The patient's own history showed only the minor ailments of childhood outside of the events recorded above. She had been married for 21 years. Her first pregnancy terminated in a miscarriage. Subsequent examination disclosed a retroversion of the uterus for which the patient was operated upon. A second pregnancy terminated at full term but the child was stillborn, delivery being instrumental. A third pregnancy resulted in a viable child which died, however, two years later of meningitis. The fourth and last pregnancy ended in a miscarriage at three months. The patient matured at the age of 10 and the menstrual function was normal and regular up to that of 15. During this interval she grew very rapidly and at the age of 14 was 5 feet 11 inches tall and weighed 170 pounds. From 15 years of age, to the time of her marriage her periods came every two weeks and were very copious. With marriage, the interval and amount again normalized. When seen by us at the age of 51 she had just passed an uneventful menopause. The patient gave a history of severe headache with her pregnancies and during her attacks of hyperthyroidism. She was at no time fatigable—in fact mentally and physically she was distinctly above the average. She had diarrhoea in the summer time but was never constipated. The remaining history was not remarkable. Physical examination showed a tall woman with high color, not excessively overweight. The bridge of the nose was underdeveloped; the teeth showed some dental attention, there was a slight residual thyroid enlargement, heart and lungs were normal as were the routine neurological findings. The skin on the lower part of the body was dry and scaly. The urine volume was normal, elimination and balance good; a small amount of sugar and increased indican were reported. The sediment was not suggestive. The nitrogen partition contained a high residual fraction. The blood showed a definite lymphocytosis but was otherwise normal. The serological tests were negative. Blood chemistry was normal; the 'phthalein test somewhat low. The patient had a greatly depressed sugar tolerance, a dose of 5 grams of galactose per os being sufficient to produce a trace of galactose in the urine. She was 14 per cent overweight and had a normal sitting height index. The lung volume was 25 per cent below prediction. Alveolar carbon

dioxide was slightly low. The basal rate was —6 per cent with a somewhat hypertensive level of the blood pressure and slightly slow pulse. The eye findings were substantially normal; examination of the fundus showed some vascular sclerosis. The pelvic examination demonstrated residua of her earlier childbearing but was otherwise normal. Radiography showed the skull and sella to be normal; the aortic arch was prominent; otherwise the chest was apparently normal.

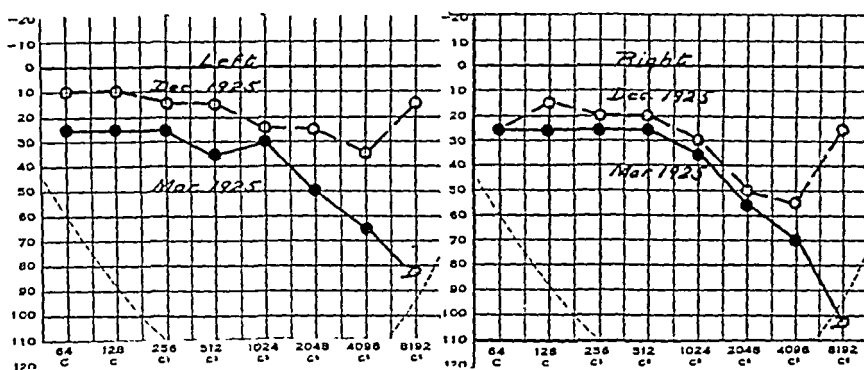
*Discussion:* While a complete resolution of this case involves a certain amount of speculation and surmise, certain points would seem to be fairly established. That the patient presented a pituitary aberration in adolescence, there can be but little question. A residuum of the posterior lobe overactivity is manifest in the very low galactose tolerance threshold. Her relatively normal basal rate must be regarded as due to the sum of the thyroid and pituitary influences. That there was an earlier thyroid overactivity must, we believe, be accepted. The operation had unquestionably lowered this activity but to what extent, it can not with certainty be said. If the pituitary disease had terminated in the usual dysfunctional formula, then the anterior lobe would be below a normal level, and this could be compensated by a residual slight overactivity of the thyroid. But it must be remembered in interpreting all basal rates that the values observed are maxima and that the true basal rate may well be definitely below that observed. The patient was an extremely intelligent woman with a sound philosophy of life. In spite of her previous medical contacts which had involved basal rate determinations she was a little nervous although controlled at the time of this test. As we saw this case a probable earlier hyperactive pituitary had in part undergone a functional involution, leaving a characteristic dysfunctional formula. Superimposed upon, and independent of, the pituitary condition a possible hyperthyroid activity had supervened. Operation had produced a dysthyroidism of relatively minor moment. If there were aberrant thyroid activity it would presumptively be on the side of some residual hyperfunction—at least of that element in the gland which influences oxygen requirement. Obviously, medication for such a condition must stress the potential pituitary state and ignore the probably less significant thyroid. There is certainly no evidence presented that would warrant further thyroid operation. On this basis anterior lobe medication was recommended and subsequent reports both from the patient and from her referring physician recorded a marked general improvement. This case presents a type of pluriglandularity in which one endocrinopathy is superimposed upon a second which had antedated it, usually by a considerable interval. The general picture, here, in the main reflected the dominant and initial endocrine disturbance. The thyroid element was an added effect, was not adequate to produce marked changes in the disease picture engendered by the primary endocrinopathy, and in its present status derived, in some measure at least, from the earlier surgical intervention. A possible alternative explanation would have been a thyroid failure of surgical origin complicating a still earlier existing bilobar hyperpituitary activity. Had this been the case the exhibition of anterior lobe medication would presumably have produced unfavorable results on the patient's symptoms. The marked betterment which she reported leads us to feel that the first hypothesis discussed offers the larger measure of probability.

CASE S-568. This patient was referred to us for deafness, of which she had been conscious for the past 3 or 4 years. The progress had been gradual and the severity somewhat variable and influenced by the patient's nervous condition. She had not experienced tinnitus nor did she show paracusis. Some years prior to her recognition of the condition she had been under a severe nervous strain and she felt that this, in part, might have been operative in determining the condition. A brother and an uncle were both deaf. She reported several cases of cardio-renal disease in near relatives. The patient's own history showed the usual minor ailments of childhood, as well as diphtheria and scarlet fever. She had the influenza in 1918 and several attacks of tonsillitis prior to a "T. & A." operation three years previously. She was occasionally constipated and when in this condition she developed nausea and vomiting. The menstrual history showed a normal onset and an uneventful history including the menopause which latter had transpired some two years before. She had been married for 7 years with one pregnancy ending in an induced abortion. She complained of dizzy spells which came at irregular intervals. The condition would last for a month or two and then she would be free for perhaps a year. Her social history included several events calculated to produce a marked degree of nervous tension. The patient was nervously unstable and markedly fatigable. A study carried out some time previous to her entry into this Clinic defined her deafness as of a toxic type and assigned the teeth, gastro-intestinal tract and, at the time of that examination, the menopause, as contributory factors. Prior to her admission the patient had experimented with small doses of thyroid and of ovarian preparation without noticeable benefit. Physical examination showed a well developed, slightly obese woman, of 55; there was a suggestion of exophthalmos and a slight edematous pouching beneath the eyes; several teeth were missing, and the remainder showed much dental attention. There was a slight struma, a slight pleuritic rub was heard in the right chest, the heart and abdomen were normal, and skin on the extremities dry and scaly. The fat distribution suggested the girdle type. The hair distribution was normal. The urine showed a normal volume, good elimination and poor balance; a trace of sugar was reported; the sediment was normal. The nitrogen partition implied an inadequate protein intake and gave a high residual nitrogen. The blood showed a somewhat low haemoglobin, a slight leukopenia, a relative increase in the lymphocytes, and a 5 per cent eosinophilia. The blood was normal in chemical composition with the uric acid relatively high. The serological tests were negative. The phthalein output and alveolar carbon dioxide were normal. She was 12 per cent overweight and nearly 30 per cent below her predicted lung volume. A fairly satisfactory basal test gave —25 per cent, a somewhat rapid pulse and normal blood pressure. The radiographic plates showed a large sella, 16 mm. x 15 mm., and a negative chest and skull. The eye examination disclosed yellowish discs, slightly enlarged blind spots, and a very slight cutting of the form field. The audiogram, herewith reproduced, showed a marked loss of hearing in the upper tones in both ears, and some diminution in the lower register. The cardiogram was normal.

*Discussion:* The case presented several points of interest. In the first place the rapid pulse, low basal rate—for the value recorded was undoubtedly above the truth—enlarged thyroid and suggestion of exophthalmos were suggestive of a thyroid failure. Equally, the lowered sugar tolerance, eosinophilia, eye findings and enlarged sella

were more in conformity with a pituitary condition. We felt that the inconsistency between the sugar tolerance and the magnitude of the basal rate could best be explained by the assumption of the existence of a true pluriglandular condition. Analysis of the entire case, however, with proper weighting of the several differential factors led to the conclusion that the pituitary influence at the time of the examination was distinctly less than that of the thyroid. On this basis it seemed desirable to attempt a therapeutic test with thyroid medication alone, and with the patient's consent this was done. The results of this treatment, which had been carried on since that time, had, in the main, been very satisfactory. The patient's hearing, as shown by the audiograms and by clinical tests, has definitely improved. A considerable amount of nervous instability has disappeared, and from the clinical standpoint there has been a definite and unmistakable improvement. It has been found expedient

PLATE III



CASE S-568

in this case to supplement the thyroid extract with some thyroxin and she has also received courses of treatment with anterior pituitary. These latter, however, have been of brief duration and we are uncertain if this latter medication has played any real part in the patient's betterment. We have recorded the case but without marked enthusiasm as one of pluriglandular involvement. It is possible that this case is essentially one of thyroid dysfunction and that the pituitary evidences were apparent rather than real.

Many of the data suggesting a pituitary involvement could equally derive from a diseased thyroid in a transition state between an initial hyper- and final hypo-activity. As was noted in our earlier paper on the thyroid (3), patients presenting this condition are not uncommon. Another possible explanation of the lowered sugar tolerance and other pituitary evidences could lie in the existence of a low-grade liver dysfunction, a condition of which certain portions of the patient's history are suggestive. While we feel that the diagnosis of uncomplicated thyroid dysfunction holds the largest measure of probability, the data as presented, in fairness warrant the tentative inclusion of this case in the pluriglandular group.

#### GROUP IIa. PITUITARY FAILURE AND OVARIAN FAILURE.

CASE B-659. This patient was referred for a group of symptoms including dizziness, numbness of the hands, dyspnoea, palpitation, and

pain in the left costal border. She was a woman 65 years of age who, at the age of 35, had had one ovary removed and at the age of 50, the uterus and remaining ovary. Seven years prior to admission, the patient then being 57, she developed intermittent attacks of numbness and tingling in the hands. Various treatments were tried but without success. During substantially the same interval she had had pain along the left costal border which was also intermittent. Dizziness, palpitation and dyspnoea had been of but one year's duration. There was a familial history of tuberculosis and of cardio-renal disease. During the patient's 13 years of married life she had never conceived although contraception was not practiced. For the 34 years preceding her admission she had worked very hard. She reported all of the minor ailments, together with diphtheria, scarlet fever, tonsillitis, and pleurisy. She recounted only the two operations noted above. Recently she had developed headaches but for many years had been troubled with pain and lacrimation in both eyes, coupled with failing vision. She was deaf in the left ear and often had pain in the right. Most of her teeth had been removed. She was markedly constipated; there was some nocturia. From her history, although her statements were not completely informative, it seemed probable that her husband had infected her with gonorrhea during her married life. The menses were established at the age of 11; the periods were regular but were always scanty. An uneventful menopause antedated her hysterectomy by five years. During the last few years she reported a steady increase in weight. Physical examination showed an obese woman in the mid-sixties, with a moderate amount of grayish-white hair, that on the body being normally distributed. The features were full and coarse. The left ear was practically deaf. There was slight hearing power in the right. The few remaining teeth were in fair condition. The thyroid was not enlarged. Heart, lungs and abdomen were substantially negative. The peripheral vessels gave some evidence of arteriosclerosis. The routine neurological findings were normal. The urines were normal in volume, the elimination good, the balance poor. One specimen showed albumin and all sediments showed much epithelial debris, but no casts were observed. The protein intake was barely at a maintenance level. The residual nitrogen fraction was high. The blood showed a slight leucocytosis with increase in the lymphocytes, while the oesinophiles were normal. The blood showed chemically, a slight upward tendency in all of the nitrogenous constituents. The serological tests were negative. The 'phthalein output was low. Galactose tolerance was 200 per cent above the patient's predicted normal. She was 52 per cent overweight and the lung volume was depressed about 40 per cent. The basal rate was —20 per cent in several concordant tests; her blood pressure was at the hypertensive level of 170/100. The pulse rates were in the lower sixties. The urea curve showed a fairly normal elimination. The alveolar carbon dioxide was normal. The radiographic study of the skull and chest was normal. A neurological report commented on the paraesthesias as reported coupled with the absence of any objective findings of significance. The heart examination determined an organ normal for her age and a tolerance for exercise reasonable for her weight. In the examiner's opinion there was no evidence of angina and he felt that the pain of which the patient complained might be due to mechanical causes connected with the lax and obese tissues. An audiogram showed marked but not complete loss of hearing in both ears. A Barany test gave normal responses. Pass pointing was within normal limits. The eye examination

showed contraction of the form and color fields to about 30°. The discs were yellow, the left blind spot enlarged and in the right eye a scotoma was demonstrated signifying involvement of the paramacula fibers.

*Discussion:* The patient's non-endocrine disease, consisting of her arteriosclerosis, hypertension, and early nephritis, obscures certain of the features of the general picture. The patient's history of surgery emphasizes one definite endocrine failure, while the laboratory findings indicate as well the presence of a bilobar pituitary failure. At the patient's age and with the non-endocrine elements in the case but little could be hoped from endocrine medication. Whole pituitary was recommended but contact was lost and we are not informed of the outcome with the case.

CASE S-744. This patient was a woman of 45 who was referred to the Clinic, presenting a progressive impairment of vision and a rapid decay of the teeth as her chief complaints. In regard to the first, she stated that she had worn glasses for 16 years, but during the last 3 or 4 years the vision had deteriorated rapidly. For many years she had been troubled with headache, which was usually frontal in character, although it occasionally involved the occipital region. These headaches occurred several times a week and were seriously disturbing. The patient had been married for 19 years, and during this time she had had five pregnancies resulting in three viable children and two miscarriages. Following the birth of the last child the teeth began to deteriorate. Six years ago both ovaries had been removed. The family history showed that the mother suffered from similar headaches; the father was diabetic and, of two living siblings, one was a chronic invalid. Three brothers and one sister had died before the age of one year. The patient's own history showed only measles in childhood, a sinus operation, an appendectomy at the time of her castration, and a dilatation and curettage after each of her miscarriages. She had been in an automobile accident eight years previously and had lost consciousness for a few moments. She was not aware, however, of any subsequent ill effects. She stated that at the age of four years she had been blind for several weeks. She was ignorant of the cause of this condition, which apparently corrected itself spontaneously. She complained of occasional tinnitus, with no loss of hearing, constipation and a susceptibility to head-colds. The catamenia was established at the age of 15; the periods had always been irregular with increase in the interval, and the flow was scanty. Physical examination showed a small woman (5 feet), well developed and slightly over weight; the hair was coarse and slightly gray; body hair distribution normal. There was a slight divergent strabismus, the teeth showed much dental attention, the pulse rate was slow, and the remaining report, including the routine neurological examination, was not suggestive. The urine volume was normal, the elimination and balance good. The urinary nitrogen partition showed a somewhat low protein intake and a normal formula. She had had a slight secondary anaemia and a lymphoid blood with slight increase in the eosinophiles. The blood chemistry and phthalein test were normal. The serological tests were negative. The alveolar carbon dioxide was slightly below the normal. The patient was 12 per cent overweight and her lung volume was slightly below prediction. The basal rate was -23 per cent; there was some lowering in pulse, blood pressure, and body temperature. The sugar tolerance was 50 per cent above her predicted level. Radiograph of the skull

showed a small, shallow and flattened sella. An eye examination showed yellowish discs and enlarged blind spots.

*Discussion:* To evaluate this case, it is, of course, essential to make allowance for the effect of her surgical hypogonadism. On this basis she presents evidences of a bilobar pituitary failure, which, added to the endocrine effect of her castration, determines a technical pluriglandular condition. Pituitary medication (whole gland) was advised.

CASE S-1327. The patient's chief complaint was of a skin eruption, from which she had suffered for several years. She also complained of severe headaches and a blurring of vision which followed spells of numbness on the left side. The patient had been married for 8 years and 3 years after marriage a tubal pregnancy necessitated the removal of one tube and the ovary on that side. Two years later an ovarian cyst was resected, and again 2 years after this the ovarian remnant and the uterus were removed. The skin eruption followed the first laparotomy, first showing as groups of small postules. For the preceding six months it had become more severe. Twenty-four years before, at the age of 11, the patient began to have spells of numbness, usually following violent exercise. At the same time a lateral hemianopsia developed, lasting for about fifteen minutes. The numbness would spread following this and last perhaps three-quarters of an hour and disappear spontaneously, leaving a severe headache as a residuum. Latterly, the spells of numbness had been confined to the left hand and left side of the body. These attacks at the time of admission were occurring at intervals of from a few weeks to several months. During them the patient never lost consciousness nor fell. The family history showed cardiac disease on the paternal side and was otherwise not significant. The patient had had various minor ailments and the influenza in 1918. She complained of occasional attacks of vertigo, some gastro-intestinal disturbance, urinary frequency during the day, and some nocturia. The catamenia was established at 13 and the history was not remarkable prior to her artificial menopause. The physical examination showed a well developed and well nourished woman in her mid-thirties. The eyes were normal, the teeth showed much dental attention, the tonsils were the seat of chronic inflammation and the anterior pillars were slightly injected. The thyroid gland was slightly enlarged. The heart showed a slight systolic murmur at the apex; there was a definite right scoliosis in the lower dorsal and upper lumbar region and marked prominence of the upper lumbar vertebrae. Some resistance and tenderness were found in the lower left quadrant. Note was made of the skin eruption confined to the chin and right cheek. The urine volumes were normal, elimination and balance good. One specimen showed a very slight trace of albumin. The nitrogen partition was normal. The blood showed a slightly low haemoglobin and a slight leucocytosis, the increase occurring in the neutrophilic elements. The blood showed chemically a relatively high uric acid. The serological tests were negative. The phthalein output was normal and the alveolar  $\text{CO}_2$  was low. The patient was 5 per cent below her predicted weight and had somewhat less than her calculated lung volume. The basal rate was observed as 15 per cent below prediction, the true rate being probably somewhat lower, as the patient was slightly nervous; earlier and less satisfactory tests had given —6 per cent and —10 per cent, respectively. The pulse was normal and the blood pressure low. An orthopedic examination defined the scoliosis as deriving from faulty

posture and of no real significance. A neurological examination failed to find evidence of organic nerve disease and the history was regarded as suggestive of migraine, as both transient palsies and hemianopsia may be associated with this condition. Endermal tests gave only negative response to a large number of food proteins. The patient's sugar tolerance was 50 per cent above prediction. A heart examination gave no evidence of disease and a cardiogram confirmed this opinion. X-ray studies of the sella, skull and sinuses were normal, as were those of the spine, pelvis and hips. The eye examination showed yellowish discs, enlarged blind spots and a possible slight contraction of the form fields. A dermatological examination defined the presenting condition as rosacea.

*Discussion:* In the evaluation of this case it is essential to remember that the patient has a definite endocrine condition of surgical origin, which inevitably influences certain of the results. For example, the low alveolar carbon dioxide and the low blood pressure should be ascribed to the hypogonad condition. With so relatively slight a drop in the basal rate, even though the true basal were not obtained, one would not normally trace a thyroid influence, certainly not one of a magnitude to produce the definitely increased sugar tolerance which in our experience is only found in profound changes of thyroid activity. The bulk of the evidence was felt to point to a bilobar pituitary failure, and this, with the patient's surgical hypogonadism, defined a pluriglandular condition. Whole pituitary medication was recommended and reports from the referring physician record a marked improvement in the patient's general picture and at the end of three months a practically complete disappearance of the skin eruption.

CASE S-1343. The patient's chief complaint, as offered by herself, was a susceptibility to infections of the respiratory tract coupled with asthma. During the past year she has been extremely fatigable and has felt that her resistance was particularly low. She ascribed this to her respiratory difficulty. During the preceding winter she had a heavy cold and a severe, persistent, productive cough. The family history was not significant beyond a record of longevity in the older generations. The patient had been married for 23 years and had borne two children without a miscarriage. Six years before admission the ovaries and uterus had been removed. She stated that she was a delicate child and had never been rugged. The history included a few minor ailments and an appendectomy 20 years before. She had hay-fever every June. She had been treated with serum for her asthmatic attacks with apparently excellent results. The catamenia was established at 14 and the menstrual history was normal up to the time of her pan-hysterectomy. Physical examination showed a fairly developed and well nourished woman in the late forties. The hair was gray and abundant. The tonsils were enlarged and inflamed. The patient stated that she had had bad tonsils for a long time, but had been advised against operation. The chest showed some dullness, scattered rales and somewhat increased focal fremitus. The heart showed a soft systolic murmur, apparently not transmitted. There was a slight mass in the right lower quadrant which the examiner ascribed to adhesions. From the patient's history as given, the appendiceal condition was bad at the time of her operation. The residual examination was not significant, including the routine neurological study. The urine volume was well in excess of two liters, the elimination good, but the balance poor; is otherwise



normal. The nitrogen partition showed a low, but adequate, protein intake with a markedly high residual fraction. The blood morphology was substantially normal except for a 14 per cent eosinophilia which was ascribed to the hay-fever and asthmatic condition recorded in the history. The blood uric acid was high. The phthalein test, alveolar CO<sub>2</sub> tension and vital capacity comparisons were all normal. The serological tests were negative. An unsatisfactory basal rate gave a level of —7 per cent. The true rate was certainly lower, although how much it would be impossible to say. The patient declined to repeat the test. She showed a hypertensive blood pressure and a somewhat slow pulse. Radiography showed the sella to be large and recorded a thinning of the wall of the posterior clinoid, presenting a picture suggestive of an hypophyseal tumor. The sinuses were normal, as was the chest. The eye examination showed moderate vascular sclerosis and yellowish discs; the right blind spot was slightly enlarged and there was a suggestion of cutting in the right form field. The patient's sugar tolerance was 100 per cent above prediction.

*Discussion:* The patient's clinical history determined ovarian failure. Superimposed upon this was an undoubted pituitary involvement. With the marked increase in the sugar tolerance and the presumptively lowered basal rate this latter condition would be a bilobar pituitary failure. The roentgenograms gave some evidence of pituitary tumor. On the basis of this diagnosis the patient falls conventionally into the pluriglandular group.

CASE S-1669. The patient's chief complaint was of recurrent temporal headaches. These started in childhood, but with the onset of catamenia they increased in frequency and severity. They had been initially unilateral in onset, but would spread over the whole frontal region in their course, which was usually three to four days. Seventeen years before admission, the patient had one ovary removed, and ten years later the uterus and remaining ovary were ablated. Since this latter event the headaches had been still more exacerbated, might be accompanied by nausea and vomiting, and were associated with pronounced mental depression. In the family history were recorded similar headaches in the father and one sister, but otherwise nothing significant. The patient had had all of the minor ailments of childhood, pleurisy following tonsillitis at 12, and several later attacks of the latter until a tonsillectomy 15 years before. She had had several brief attacks of mild generalized arthritis. She had worn glasses for many years without influencing her complaint. Her appetite had been fair, with the voluntary elimination of sweet and rich foods from her dietary. She was severely constipated and had been troubled for years with hemorrhoids. The catamenia had been established at 12, was at first irregular, but after some two years became regular with somewhat shortened rhythm. The flow was normal in amount. An uneventful menopause had occurred some six months before her hysterectomy, which was for a fibroid tumor.

The physical examination showed a well-developed and nourished woman of 51, with slight pilosity on the upper lip, but other hair distribution normal. The remaining findings were completely normal. The urine volume was ample, the balance of the observations not significant, except for a high residual nitrogen fraction. The blood showed a lymphocytosis and slight (35 per cent) eosinophilia. The blood uric acid was relatively and absolutely high, the serological tests were negative, and the phthalein output and CO level normal.

She was at her predicted weight, but appreciably below (36 per cent) her calculated lung volume. A fairly satisfactory basal rate measurement was 12 per cent below prediction, with somewhat lowered pulse and blood pressure. X-ray plates showed a large sella and obstructed nasal fossae, but otherwise normal findings. The sugar tolerance was 100 per cent above her normal level. The eye examination showed yellow discs, enlarged blind spots, and some cutting of the fields, more marked in the left eye.

*Discussion:* The picture given above defines a bilobar pituitary failure, with but few of the conventional evidences lacking. In addition, there is superimposed a surgical hypogonadism, making the diagnosis technically pluriglandular failure.

### GROUP IIIa. THYROID FAILURE AND GONAD FAILURE

CASE S-686. This patient was a girl of 19, who complained of frequent headaches in the frontal and supra-orbital region, from which she had suffered for about a year. A recent eye examination had failed to disclose any cause for this complaint, and she had been referred for an endocrine study. She also complained of a pain in the sacro-iliac region. She became dyspneic on the slightest exertion and was very fatigable. The family history was entirely irrelevant. The patient's own history showed a few minor ailments and a tonsillectomy and adenectomy some two years before. She had been married in the fall of the preceding year and had aborted an early foetus inside of three months. She described her headaches as sharp in character and aggravated by pressure. The face became flushed and there was a general feeling of malaise. The frequency varied from every other day to once a week, and their incidence was apparently not associated with any other event. She had several sore-throats since her tonsillectomy. She complained of intervals during which the nipples become red and sore and were painful. The menses began at the age of 14, were regular, and the periods apparently normal. Physical examination showed a well-developed, somewhat undernourished girl. There was a slight tenderness over the frontal sinus, poor occlusion of teeth and numerous small papules on the areolae of both breasts. The chest and abdomen were normal, and the remaining examination not informative. The urine volume was normal, elimination and balance poor; albumin was recorded, but the sediment was normal. The residual nitrogen was somewhat above the normal. The blood showed a slight but definite secondary anaemia with a slight lymphocytosis. The blood chemistry was normal; the serological tests were negative, the phthalein output somewhat low. The patient was 10 per cent under weight and the lung volume was somewhat below prediction. The basal rate was 29 per cent below the normal, and the pulse, blood pressure and temperature all definitely low. The sugar tolerance was 25 per cent below prediction. Alveolar carbon dioxide was a low normal value. Radiographs of the skull were normal. A pelvic examination disclosed a resistant mass in the region of the right adnexa, which was interpreted as either a cystic ovary or hydrosalpinx. The eye findings were normal.

*Discussion:* At the time this case was studied it was felt that the urine picture and the basal rate determined a thyroid failure, while the lowered sugar tolerance, coupled with the results of the pelvic examination, were interpreted as indicating some degree of ovarian failure. In the light of later experience it seems doubtful if this case warrants a pluriglandular diagnosis, as the dysfunctional state of

the thyroid (transition) would probably account for all of the departures from the normal. In view of the fact, however, that there was tangible disease apparently associated with one ovary, we have felt that in fairness this case should be retained as presenting a possible multiple glandular involvement.

**CASE B-109.** The patient's presenting complaint was given as indigestion, and the duration of the illness as 18 years, the condition following a bilateral oophorectomy. The family history gave the death of the parents as from cardio-vascular disease; one of four sisters had hyperthyroidism; and one of five brothers died of hydrocephalus at eighteen months. The patient had been married for over 20 years, had borne one child and had one miscarriage and one ectopic pregnancy. She had had the usual illnesses of childhood, together with diphtheria, broncho-pneumonia 10 years previously, influenza at the time of the epidemic and cystitis several years before. She complained of occasional headaches, vertigo, and fainting spells. These latter she traced to peculiar sensations which would occur in her laparotomy scar. She reported occasional spasms of the epiglottis. She was greatly troubled with nausea and vomiting, which would occur usually an hour after eating. The bowels were constipated; there was some nocturia. The catamenia was established at the age of 16, was always irregular with increased interval and scanty flow until her operation terminated the function. Prior to her hysterectomy, a nephropexy had been performed and 8 years after she was operated upon for lysis of adhesions and had an appendectomy. Physical examination showed a well-developed and somewhat undernourished woman, nervous and garrulous, of about 50 years of age. The hair was thick and soft and that on the body was normally distributed. The teeth showed much dental attention; the thyroid was not enlarged; the lungs and heart substantially normal, and there was some tenderness in the right lower quadrant. The remaining examination was not significant. The urine volume was normal, elimination and balance poor; albumin was recorded, and the sediment showed much epithelial debris, numerous leucocytes and a few blood discs. The residual nitrogen fraction was positively high. The blood showed a marked lymphocytosis. The blood chemistry was normal except for a somewhat high blood sugar which was not verified on subsequent examinations. The serological tests were negative. The phthalein test was normal. The sugar tolerance was normal for one with the patient's gonad deficiency. Alveolar carbon dioxide was definitely low. The patient was 14 per cent under weight and with a somewhat depressed lung volume. The basal rate was —30 per cent, with low blood pressure, slow pulse, and somewhat low body temperature. The urea curve was normal. The eye examination showed slightly enlarged blind spots, but otherwise normal. X-ray plates showed a normal skull and sella, together with normal heart and lungs. A gastrointestinal series of plates was normal. A pelvic examination gave results in accordance with the patient's history. A genitourinary examination defined an existing cystitis. A neurological examination failed to disclose evidence of organic nerve lesion. The patient had had, however, psychotic episodes in the past, was distinctly psycho-neurotic at the time of her examination, and some time after her discharge had an acute psychotic episode.

*Discussion:* Analysis of the data here demonstrates a thyroid failure superimposed upon the surgical hypogonadism. Naturally, with the patient's stormy surgical history, the bladder condition, and

the mental and nervous instability, the picture lacked the clarity of outline of an uncomplicated thyroid failure. Thyroid medication was advised and for a time was followed with marked evidence of clinical improvement. Later contact with the patient has been lacking.

**CASE B-599.** The patient was a woman of 54 complaining of headaches and of fatigability. The former condition had obtained for the preceding three years, occurred at intervals of approximately four weeks, and lasted from one to three days. The pain started in the left occipital region and usually extended forward to the left parietal or even the left frontal. It also radiated downward to the shoulder and arm. Simultaneously there was pain in both feet in the region of the arches. The rhythmic occurrence of the headache would suggest an association with the menstrual cycle which, however, was denied by the patient's history. The menses had been established at the age of 14, and six years later a pan-hysterectomy was performed. The inference drawn from the history was that this somewhat drastic method was adopted to correct extremely painful and debilitating periods. An interesting statement made by the patient in connection with the headaches was that they were always preceded by a period of "black rage," caused by some trivial event, and that they were always followed by periods of profound exhaustion. The family history was not significant. The history included the minor ailments of childhood, attacks of rheumatic fever at 16, at 20, and at 30, the last of these being followed by an arthritis of several years' duration, but without apparent cardiac complications. There had been several nervous breakdowns during the patient's life. She had had abscessed ears requiring operation. At the age of 7 she was struck on the head by a railroad gate and was rendered unconscious for several hours; again, at 14, trauma to the head caused another period of unconsciousness. Beside her hysterectomy she had had a gall bladder operation 8 years previously and, more recently, a tonsillectomy. She had been over weight for a number of years, a condition only partly controllable by dieting. She stated that she was nervously unstable, easily frightened and tended to be irritable. At the age of 12 she had a severe attack of psoriasis, which lasted for about a year and a half. She apparently had a food sensitivity to eggs. Physical examination showed a somewhat obese woman in the middle fifties. She was moderately deaf, but the remaining findings were practically normal. The urine volumes were normal, elimination was fair, the balance poor and the remaining examination negative. The nitrogen partition was normal. The blood showed a slight secondary anaemia and was definitely lymphoid. The blood chemistry was normal; the serological tests were negative; the phthalein output was normal. The sugar tolerance showed a negative response to 20 grams and a positive response to 30. This would indicate an increased tolerance for one in the patient's gonadal condition. She was 31 per cent overweight and had lost nearly half her predicted lung volume. The urea curve was normal. Alveolar carbon dioxide was at a normal level. Her basal rate was reported as —21 per cent, with low blood pressure, pulse rate, temperature and respiration rate. The patient was outwardly calm, but confessed to a definite nervousness, evidence of which she had concealed. A pelvic examination gave results in harmony with the patient's earlier history. An endermal test showed a negative response to egg albumin. A nose and throat examination showed a slight septal deviation. X-ray examination of the skull showed a slight elevation of both tables, posterior to the junction of the coronal and sagittal sutures; the sella was small

and regular; the frontal sinuses were irregular and blurred in outline, a condition consistent with an old sinusitis. The audiogram showed a loss of hearing in both ears, more pronounced in the higher frequencies. The eye examination showed normal fundi, enlarged blind spots, and a marked cutting of the upper form field demonstrably due to drooping lids. The neurological examiner commented on the evidences of an earlier frontal sinusitis and possible fracture of the skull in childhood, but failed to discover any evidence of organic disease.

*Discussion:* Taking the results produced by the patient's castration, it is obvious that a second possible endocrinopathy is superimposed on the surgical condition. With the increased sugar tolerance and moderate depression of the basal rate, one would instinctively think of a pituitary failure as the underlying functional endocrinopathy. The history of the blow to the head would also turn attention in this direction. Further analysis, however, makes the case for the pituitary much less certain. The physical findings associated with the basal rate determination are of the lower order of thyroid and not that of pituitary failure. Again, the blood shows only a lymphocytosis, there being no increase in the eosinophiles. The blood uric acid was normal. The basal rate was at least 21 per cent below prediction and there was every probability that the true rate fell somewhat below this. The sugar tolerance would seem to offer a stumbling block since there is a definite increase here wholly disproportionate to the magnitude of any probable thyroid failure. This patient was castrated within six years of the establishment of the menstrual function and thirty-four years before the time of study. As one of us has reported elsewhere, opportunity had occurred to study another patient who, like the present one, had been castrated at a very early age and many years before the study was carried out. She, too, showed a sugar tolerance of 30 grams. It seems possible, although the suggestion is offered only tentatively, that with early castration and the subsequent lapse of several decades, some sort of a compensatory process might have come into being. Another possible explanation could be that the thyroid failure was of such a magnitude as to condition an increased tolerance. While the lowering of the basal rate was of very moderate proportions, the value observed was certainly above the truth. Whether this assumption be correct or not, the present patient patently presents an endocrine disorder superimposed upon her surgical hypogonadism. The thyroid seemed to us more probably at fault, and the opinion was offered on that basis. The controlled use of thyroid medication was recommended.

CASE B-662. This patient came for study complaining of overweight, although she was 8 per cent below prediction. Subsequent knowledge of this fact by the patient did not influence her earlier conviction. She also reported herself as markedly fatigable and she complained of a swelling of the hands and wrists. She dated all of her complaints from the birth of her only child, an event that had taken place some 11 years before. She was delivered by Cæsarean section and at this time a pan-hysterectomy was performed. Within a few weeks of her operation she was obliged to take a long and fatiguing journey, and shortly after this her hair began to fall out. Under treatment this condition was corrected. Prior to her successful pregnancy the patient had frequently conceived, but had uniformly induced abortion, the total number of which she had forgotten. The family history included cardiac disease in both parents, tuberculosis

in a surviving brother and several other brothers who died in early infancy. In her own history, she reported minor ailments in childhood; a very severe case of influenza during the War, which she was told left her with an impaired heart, and a record of several nervous breakdowns. For a short time in the previous year she had suffered intermittently from precordial pain, but had had no attacks recently. She stated that she had a large appetite and, in the main, a perfectly functioning alimentary tract. Under the stress of nervous excitement, however, she had a tendency to vomit. She established the menses at the age of 11, and the function continued normal and regular until her castration. Physical examination showed a well-developed woman in the earlier forties. The hair was somewhat scanty, that on the body showing a normal distribution. Percussion demonstrated a possible cardiac enlargement; the blood pressure was definitely low. There was tenderness in both lower quadrants of the abdomen and some question of the tendon reflexes. The urine volume was normal, elimination fair, balance poor; albumin was recorded, but the sediments were normal. Her protein intake was below a maintenance level; the nitrogen partition formula was substantially normal. The blood showed a slight secondary anaemia, a distinct lymphocytosis, and a slight eosinophilia. The nitrogenous constituents of the blood were all slightly above normal, the uric acid showing the smallest relative increase. The serological tests were negative. The phthalein output was below normal, the sugar tolerance normal. She was 8 per cent underweight, with a substantially normal sitting height index. The lung capacity was unimpaired. The urea curve showed fair elimination. The basal rate was —25 per cent, with marked depression of the blood pressure and temperature and a somewhat slow pulse. A heart examination gave no evidence of organic disease nor did the cardiogram, failing to confirm the earlier reports. In the examiner's opinion her cardiac symptoms were of functional nervous origin. The neurological findings were normal, failing to confirm the findings earlier reported. A pelvic examination yielded results in accordance with the patient's history. The eye examination showed some vascular sclerosis and otherwise normal findings.

*Discussion:* The patient was a markedly neurotic individual, presenting in a striking degree the insistent egocentricity of the gonad failure. She was wholly incooperative, a fact which influenced some of the tests and precluded the securing of others. She was wholly disingenuous in regard to her history; such statements as we have recorded above are, so far as we know, fairly accurate. There was no question that there was a surgical hypogonadism. Superimposed upon this was a second endocrine defect. With the level of her basal rate, with the normal sugar tolerance, the evidences of lowered kidney permeability, the normal eye findings, to name but a few, the thyroid seemed to be the most probable focus of failure. Thyroid medication was advised. This case falls technically into the group of pluriglandular syndromes. Its multiple character, however, derives from the surgical operation.

CASE B-976. This case presents unusual points of interest, as it gives the details of the study of a male castrate with a second superimposed endocrine defect. The patient was a man 67 years of age who gave as his chief complaint a sexual disorder. The history showed that 35 years previously (November, 1892) he had had a fall from a bicycle and struck his head and was rendered unconscious for several hours. He had a few days of convalescence and then re-

turned to work, apparently none the worse for the experience. Six months later he began to be troubled by indigestion associated with nervous exhaustion and occasional fainting spells. At about this time he found that sexual intercourse had become distasteful and was followed by a dull headache. In a very short time he lost all sense of desire. He was placed under treatment and began to improve. With his improvement sexual desire returned, but there was premature ejaculation, and this disturbed him greatly. He had been married some two years before his accident and his wife had borne one child, a daughter. The unsatisfactory character of his marital relationship gave rise to a marked emotional instability that seemed to amount to a psychoneurotic condition consisting mainly of a phobia of sexual intimacy. Two years after the accident he had a small hydrocele, and this was corrected with removal of the testicle. A year later he was advised to have the other testicle removed to correct the mental condition, and in the face of opposition by a consulting physician complete castration was performed. This second event was in 1898, or 30 years before his admission for this study. Between 1898 and 1901, rest and treatment by a neurologist gradually brought about some improvement. As a result, he was able to resume work and to re-establish his financial independence. This later condition obtained from 1901 to 1914; there was some continued improvement, and the occasional severity of the nervous instability did not prevent employment. Again, two years later, he developed urinary symptoms and cystoscopy demonstrated a stricture. Dilatation with sounds produced some betterment. A year later the verumontanum was removed. Following this operation he had a phlebitis in the left leg. In spite of his gonad defect, for a number of years close association with women had produced marked reactions which he called sexual disturbances. During this interval he had been aided somewhat by psychoanalysis and in 1923 a course of steam baths brought temporary relief. A course of treatment with orchic material was followed by a recurrence of the earlier symptoms and led to a discontinuance of the therapy. Subsequent to this he was given a brief course of thyroid therapy which, as it was based on basal rates which were always reported as within the normal range, never exceeded a dosage of more than one grain a day. This treatment yielded no result, and two years prior to admission to this Clinic the patient had come under the control of a clinical psychologist who had produced very marked improvement in the neurological and mental picture. As there were obviously physical difficulties as well, our study was undertaken to ascertain the patient's functional level. It should be mentioned in passing that the reason given for the second orchidectomy was to eliminate pain in the pudic nerve. The family history showed a rather remarkable longevity in his immediate relatives and one case of epilepsy in a brother. As noted above, he had been married and his wife had borne one child prior to his mutilation. He reported relatively few ailments outside of those recorded above. "Inflammation of the bowels" at 16, mild diphtheria at 20, and several traumatic injuries to the extremities were reported. He complained of head pains starting in the occiput and radiating forward, but not of true headaches. There had been some loss of hearing in the left ear. His teeth had always been poor, and while under his endocrine medication he had periods of "nerve aching" in the jaws. During his long illness there had been brief periods when he was slightly jaundiced, and he complained of more or less gastro-intestinal disturbance for the preceding four decades. He recorded tenderness along the course of the sciatic nerve, also tenderness on both sides of the lumbo-sacral spine.

Throughout his illness he stated that he had been very nervous and irritable and was introspective, readily excited and emotional. The psychologist found a history of anxiety neurosis, but there was no hallucinations or delusions. He had been markedly fatigable for many years. Physical examination showed a well-developed and nourished man with a tendency toward obesity in the abdomen and chest wall. The protuberant abdomen determined a poor posture, increasing the lumbar lordosis. The hair on the vertex was steel gray and moderate in amount. The pupils showed a sluggish light reaction and a beginning arcus senilis was noted. There was apparently a bilateral deafness. The teeth were in fair condition, the tonsils apparently not offending. The heart, lungs, and abdomen were normal. The penis was short and small, the scrotum small and empty. The sparse pubic hair was of female distribution. In addition to the lordosis noted above, there was a moderate right lumbar scoliosis, a tenderness on palpation at the levels of the seventh thoracic and about the lumbosacral joint; also some tenderness on pressure in the right portion and along the courses of the sciatic nerves. The cranial nerves were intact. The normal reflexes were active. The train and content of thought were normal, and the routine neurological findings otherwise normal. The urine volume was normal, elimination fair, balance good. Albumin was recorded in both specimens. The nitrogen partition showed a somewhat high residual fraction. The blood showed a slight but definite secondary anaemia. There was a relative increase in the endothelial leucocytes and a slight relative increase in the eosinophiles. The nitrogenous constituents of the blood were all slightly above the normal. The serological tests were negative. The phtkalein was definitely low. Galactose tolerance was somewhat depressed. He was recorded as 14 per cent overweight, but was actually in excess of this, as the sitting height index was high. There was a perceptible loss of lung volume. Alveolar  $\text{CO}_2$  was at a normal level. An urea index was a low normal value. The basal rate was 30 per cent below predication, with bradycardia, sub-normal temperature, and low blood pressure. A genitourinary report indicated normal conditions. Repeated examination of the patient's stools showed no parasites, ova or blood. An ear examination gave normal findings. The audiogram showed loss of hearing, which was more pronounced in the upper register. The Barany test findings were normal. The blood fragility was normal. A neurological examination gave no evidence of organic disease. A cardiogram was substantially normal. The eye examination showed normal pupillary reaction, yellowish discs, some vascular sclerosis, and a cutting of the upper form field, due to drooping lids. An orthopedic examination confirmed the existence of a low back-strain. Radiography showed a proliferating arthritis of the right astragulo-scapoid articulation; the right sacro-iliac joint picture was hazy and indistinct, and there were asymmetrical articulations in the 4th and 5th lumbar region. There were hypertrophic spurs on the dorsum of the right foot. The skull, sinuses, and sella were normal. The teeth were not diseased. A gastro-intestinal examination gave normal findings. A Graham test by the intravenous route was also normal. The patient had a slight skin eruption on the lower left leg which was defined in a dermatological examination as a mild erythematous eczema. The icteric index and Van den Bergh tests gave normal findings, but an examination of the duodenal contents by the McClure technique showed a marked liver dysfunction. A very full statement of the mental aspects was made available through the courtesy of the referring psychologist. It does not lend itself, however, to presentation in abstract form.



*Discussion:* Experience with other male castrates has demonstrated that the condition produces but minor changes in the level of vital function tests. With due recognition of this fact, the picture presented by this examination shows a clear-cut thyroid failure of considerable magnitude and probably of long duration. The demonstrated liver dysfunction explains the somewhat lowered sugar tolerance. Apparently this difficulty was confined to the liver and did not include the gall bladder. An interesting feature in this case is the failure of the lowered thyroid activity to produce a lowered sexual level. That his sexual abnormality, however, was confined to the mental reactions and secondary sexual emotions and was probably engendered in part, at least, by psychogenic factors, explains in some measure the presenting anomaly. In our experience, male castrates are relatively rare, at least those who are willing to undergo investigation. We feel particularly fortunate in the opportunity to have studied this case, which conventionally falls in the pluriglandular group.

CASE S-1843. The patient's chief complaint was of ready fatigability, coupled with pain over the sternum and radiating to the left shoulder. She was also extremely nervous. The patient was 48 years of age at the time of the study and had matured at the age of 17. The periods were very irregular, with both increase and diminution in the interval. The flow was profuse. Three years and a half before admission she flowed steadily for a period of six months. Operation was recommended and the ovaries and uterus removed. Up to that time the patient's health had been good. Her present difficulties, she felt, dated from the operation. Within the preceding six months the pain and a numbness of the fingers of the left hand had developed. The family history included that of the mother's death of cancer, the father's from gangrene. The patient had been married 30 years, had always desired children, but had never conceived. She reported only minor ailments, pneumonia at the age of 5, and a nasal operation many years before. Fifteen years previously she had been struck by an automobile, and although she sustained no fractures, was placed in a jacket for a few months; she had shown no symptoms subsequently. Some six years before she began to have severe headaches, but these disappeared after her operation. For a number of years there had been a gradual loss of hair and slow, progressive impairment of vision. For the past few years she had had occasional attacks of dyspnoea. She had a tendency to constipation and stated that she found it necessary to remove the feces manually. Her physical examination showed fair development and nourishment, some thinning of the hair on the vertex, and body hair normally distributed. The eyes were normal. The tonsils were open to suspicion. There was no thyroid enlargement. Heart, lungs and abdomen were normal. The skin was dry and atrophic and there was some hypertrichosis on the upper lip and chin. The routine neurological findings were normal. The urine was scanty, the elimination and balance poor. The nitrogen output indicated an inadequate protein intake; the partition formula was substantially normal. The blood showed a lymphocytosis and a slightly high value for the nitrogenous constituents; the serological tests gave normal findings. The 'phthalein output was below normal; alveolar CO<sub>2</sub> at a normal level. She was recorded as 4 per cent below her predicted weight, with a significant loss in predicted lung volume. The basal rate was —24 per cent. The sugar tolerance was normal for her castrate condition. The pulse and temperature were distinctly low. The blood pressure showed an upward tendency,

although falling far short of a hypertensive level. A nose and throat examination showed a minor septum deviation and unoffending tonsils clearing the earlier finding. A cardiogram confirmed the bradycardia and was otherwise negative. The eye examination showed poor convergence accommodation, marked cutting of the upper form fields from lid droop, and slightly enlarged blind spots.

*Discussion:* In addition to the surgical hypogonadism, the patient had a fairly typical thyroid failure, without myxedema, which was probably of long standing. Technically, the case is pluriglandular. It would be interesting to speculate on what would have been the influence of thyroid medication on the excessive menstrual flow which led to the patient's castration.

### GROUP III-b. THYROID DYSFUNCTION AND GONAD FAILURE

CASE S-179. The patient's chief complaint was of weakness and dyspnoea. The condition followed operations in two stages for the partial removal of a hyperactive thyroid. After the second operation the patient had gradually become fatigable and developed a lack of strength. She had been much underweight as a result of the earlier toxic thyroid and had gained 40 pounds in the interval. During the past two years she had been greatly troubled with hot flashes and had noted coincidentally a marked diminution in the menstrual function. Previous menstrual history showed maturity at 12 and a regular rhythm with somewhat excessive flow. She had been married 17 years and had borne two children without miscarriage. Her family history was not relevant. The patient had had minor ailments, together with scarlet fever at 16, typhoid at 18, the two thyroid operations already noted, a ventral suspension of the uterus, and two repair operations on the vagina. She stated that her teeth were very sensitive and required constant care. The year before she had had a brief attack of indigestion. The bowels were regular. Recently she had developed a slight vulval pruritus. Physical examination showed good development and nourishment. The patient was somewhat slow in her physical and mental response. The skin was moist, the hair normal in amount and distribution. There was no residual thyroid enlargement. The heart, lungs, and abdomen were normal, as were the structures considered in a routine neurological examination. The urine volume was normal, elimination and balance poor; the findings were otherwise normal. The nitrogen partition examination showed an inadequate protein intake and a normal formula. The blood showed a slight leucocytosis, with increase in the neutrophilic elements. The blood was normal chemically. The serological tests were negative. The 'phthalein output was somewhat below normal; alveolar carbon dioxide was definitely low. The patient's observed weight corresponded with prediction. There was some lessening of the lung capacity. The basal rate was reported as —11 per cent, with a slightly rapid pulse, a slightly febrile temperature, and a very low blood pressure. Radiography of the skull, sella and chest showed all these structures to be normal.

*Discussion:* It is a question in our minds whether this case properly belongs in the pluriglandular group. There is patently a thyroid dysfunction dating from the earlier overactivity. The history of the recent pruritus suggests a possible glycosuria, although the specimen of urine examined was sugar free. The blood pressure was very low. The alveolar carbon dioxide was below the normal. Additional opportunity for observation was requested on this patient, but could not be

secured. While we do not regard the case as clearly belonging to the pluriglandular group, we feel that there are enough evidences to warrant the suggestion of a gonad failure superimposed upon the thyroïd condition.

**CASE S-230.** This patient offered an interesting study, as both of her two endocrinopathies existing at the time of study had surgical backgrounds. Sixteen years before admission the patient noted a glandular enlargement in the neck. Medical consultation defined a cardiac insufficiency, and the patient was hospitalized for rest. During her stay in the hospital she was given tuberculin for the glandular condition. This treatment produced no result, and subsequent x-ray treatment was ineffective. Three years before her admission to this Clinic the neck condition was diagnosed as a goiter and a portion of the gland removed. At about the same time she was also operated upon for a uterine fibroid and a bilateral ovariectomy was also performed. Prior to the removal of the thyroïd the patient experienced no symptoms which she felt could be referred to the condition. The family history was negative. The patient had had the usual childhood diseases, and rheumatic fever 35 years before. The menstrual history was entirely normal up to the time of her laparotomy. Her remaining history was entirely negative. The physical examination showed a well-developed and somewhat obese woman of 48. Beyond the scars of her two operations the only point of significance lay in a systolic murmur at the apex of the heart which was transmitted to the axilla. There was apparently an aortic insufficiency and regurgitation. The urine volume was scanty; elimination and balance were poor. The urine contained less than a gram of sugar and was otherwise normal. The blood was markedly lymphoid, and there was a slight secondary anaemia. The blood was normal, chemically. The serological tests were negative. The 'phthalein output was normal. Her alveolar CO<sub>2</sub> was of normal value. The patient was 20 per cent overweight and about 30 per cent below her predicted lung volume. A fairly satisfactory basal rate was 6 per cent below prediction, with a somewhat low blood pressure, normal pulse and temperature.

*Discussion:* There can be no question in this case as to a lowered gonad activity, but the level of the thyroïd function cannot be so simply resolved. It would seem probable that the lowering of the basal rate produced by castration was compensated by a residual slight hyperactivity of the thyroïd. The lowered sugar tolerance was referable to the gonad condition. Its principal interest, in our opinion, lies in the slight departures from the normal produced by two mutilating operations which produced a condition in which there was a very definite degree of mutual compensation.

**CASE S-988.** The patient's chief complaint was of intense nervousness and fear, coupled with difficulty in breathing, excessive perspiration, and palpitation. She had a very marked thyroïd enlargement and was somewhat obese. The mother had a goiter which began at the age of 25, and when the patient was 23 (26 years ago) she noted that her own thyroïd was beginning to enlarge. It grew slowly for a number of years, then remained stationary for a still longer interval, but had begun to grow again in the preceding three years. With this second growth period the majority of her symptoms had developed. The choking sensation in her throat was one of her principal difficulties. She had been obese for a number of years. Some 10 years before both ovaries had been removed and her obesity

apparently began after this operation. The family history, outside that of the mother, showed only diabetes in an uncle. The patient had been married for 20 years and had borne two children without miscarriage. The additional records showed only minor ailments, recurrent sore-throats, an occasional dull headache, and some loss of vision. She believed that the eyeballs had protruded slightly during the last few years. A tonsil and adenoid operation a number of years ago had diminished but not eliminated her tendency to sore-throat. The gastro-intestinal history was not suggestive. The menses were established at 15 and were always irregular with an erratic rhythm. Physical examination showed a moderate obesity. There was some difficulty in breathing, a slight suggestion of exophthalmos, hypertrichosis on the lip and chin, excessive pilosity on the limbs, but female distribution of pubic hair. There was marked thyroid enlargement and forward or backward movement of the head produced difficulty in breathing. The heart and lungs were normal. There was an ill-defined tenderness in the abdomen on deep pressure. The extended fingers showed a fine tremor. The urine volume was slightly low; elimination and balance were poor. Albumin was recorded; the findings were otherwise normal. The protein intake was ample; the residual nitrogen fraction much above the normal. The blood showed a slight secondary anaemia and a 66 per cent lymphocytosis. The blood analysis showed slight increase in all of the nitrogenous constituents. The serological findings were normal. The phthalein output was low, and the alveolar carbon dioxide, normal. The patient was 36 per cent above her predicted weight and 40 per cent below her predicted lung volume. The basal rate was  $-13$  per cent, with a somewhat rapid pulse and lowered blood pressure. Radiography showed a normal sella and normal mediastinal shadow. An examination of the mouth showed many dubious teeth, heavily crowned. A nose and throat examination showed hypertrophied, infected tonsils and a non-obstructing septum deviation. A neurological examination disclosed no abnormalities. The eye findings were practically normal. Her sugar tolerance was depressed slightly below the level conditioned by her castration. A repetition of the basal rate a few weeks later gave a level of  $-1$  per cent, with a somewhat more rapid pulse.

*Discussion:* The patient's surgical hypogonadism determines one factor in her pluriglandular definition. She also had a definite thyroid enlargement which we were inclined to believe was in a dysfunctional state. If the thyroid were slightly overactive it would exercise a compensating influence in the lowering effect of the castration. It would also account for her lowered sugar tolerance, as has been noted at length in an earlier thyroid paper. While again the case is not clear cut, the bulk of evidence pointed to a thyroid dysfunction superimposed upon a surgical hypogonadism. Both were of long standing. The patient was not regarded as a suitable subject for operation at the time, but was advised to remain under observation in anticipation of a change in the level of thyroid activity. Iodine medication was suggested. A year later the patient returned for a repeated study and showed almost identically the same picture as that first presented. The significant changes were a loss of some 13 kilograms in weight, an increase in the evidences of kidney impairment, and a definite increase in the thyroid size. In spite of these disadvantages, the patient reported herself as feeling very much better, except for increased difficulty in breathing. There was no change in the relative basal rate. Operation was recommended with a view to correcting mechanical interference with breathing, and a large tumor mass was

removed which was reported by the pathological laboratory staff to be a colloid goiter. The patient is to return for further study in the near future.

CASE S-1023. The patient's chief complaint was of deafness, coupled with flatulency, vomiting and gastric discomfort without pain. This condition had developed some 10 years before admission, at the time of her marriage at the age of 29. The condition was progressive for some 5 years, and 3 years ago an operation was performed for lysis of adhesions. No immediate improvement was manifested, but after a few months she improved definitely and the vomiting became very infrequent. Eighteen months before, however, she began to vomit once or twice a week, gradually increasing in frequency to three or four times a week. On one occasion the vomitus contained fresh blood. More recently, intermittent pain in the right hypochondrium had developed and also in the right lower quadrant. The bowels showed alternating periods of constipation and diarrhoea. The family history was entirely normal. The patient had been married for 10 years without pregnancy. Subsequent questioning developed the fact that she had had both ovaries removed 24 years before, at the age of 15. We could not ascertain the reason for this operation. She offered the usual history of minor ailments, an appendectomy at the time of her ovariectomy, and influenza during the epidemic. She complained of an occasional headache. Her deafness was of about 13 years duration, had been progressive and accompanied by tinnitus, vertigo, and paracusis. The history, while not clear cut, offered some evidence of an earlier otitis. She was subject to head colds, had a nasal obstruction, had had a pyelitis in the previous eighteen months; this had yielded to treatment. The catamenia had been established at 11, and was regular and scanty up to the time of her artificial menopause. Physical examination showed fair development and nourishment. The hair on the vertex was thin and coarse; there was no marked hypertrichosis. The aural acuity was distinctly impaired. The thyroid was not enlarged. The heart, lungs, and abdomen were substantially normal. There was a minor cervical adenopathy, some tenderness in the mid-dorsal region of the spine, and normal routine neurological findings. The urine volume was normal; elimination and balance, poor. Albumin was reported. The nitrogen partition was normal. The haemoglobin was low, the blood cells normal in relative numbers. The blood showed high uric acid, which was not confirmed by later examinations. The 'phthalein,  $\text{CO}_2$ , and vital capacity measurements were substantially normal. The serological findings were normal. An unsatisfactory basal examination showed—14 per cent, with rapid pulse, a slightly febrile temperature and a downward tendency to the blood pressure. Eye examination showed enlarged blind spots and a slight contraction of the color fields. The audiogram showed marked loss of hearing in both ears. The patient's sugar tolerance coincided with the level produced by castration. A radiographic series of gastro-intestinal plates was normal.

*Discussion:* This case presented several points of obscurity. When the patient was first seen the lowered sugar tolerance, the high blood uric acid (subsequently found to be in error), and certain points in the history suggested a possible pituitary condition. Additional observations were requested in the course of these, and as the result of questioning, the patient told of her castration at the age of 15. As stated above, we could not learn the cause of this operation, but the fact that it had taken place naturally influenced the interpretation

of the findings. Some additional measurements were secured, although not all that were requested. The patient had a definitely low basal rate, although we could not ascertain its real magnitude. It was felt that there was some evidence for the existence of a possible thyroid dysfunction complicating the surgical hypogonadism. The patient was not entirely cooperative, and it has been impossible to verify the tentative conclusion. The case is offered as one of a somewhat doubtful pluriglandularity in which gonad failure is established and the thyroid disturbance a matter of possibility.

**CASE S-1069.** The patient's chief complaints were of a general fatigability, palpitation, and arthritis. Four years before admission she developed an acute attack of arthritis, localized in the left hand and complicated with a cystitis. Under treatment both conditions cleared up in about six weeks. Following these, her fatigability developed. There had been an earlier history of arthritis, somewhat obscure in definition, and generalized as to distribution. The patient had been troubled with sore-throats, but these had yielded largely to a tonsillectomy 2 years before. For several years the teeth had also been a cause of difficulty and a year previously three had been removed, all of which showed abscessed roots. She had had palpitation for the past three years and occasional attacks of precordial pain during the last year. The family history was not especially significant. The patient had been married for 20 years and had borne two children without miscarriage. In addition to the minor childhood complains, she had had small-pox when three months of age. Her surgical history included a repair operation, the removal of one cystic ovary, and, later, a complete castration, an appendectomy, and two tonsillectomies. She had been subject to headaches, but these had been helped somewhat by glasses. There was some loss of hearing in the left ear, and some obstruction of breathing on the left side. She experienced considerable vascular disturbance after the removal of her second ovary. She was constipated and had worn a brace for 15 years for gastroptosis. The menstrual history was not remarkable. She complained of trouble with the sacro-iliac joint for the past 16 years. Her physical examination showed good development and nourishment and substantially normal conditions throughout. The urine volume was normal, elimination and balance poor; albumin was recorded. There was a high residual nitrogen fraction. The blood showed a low haemoglobin and marked lymphocytosis. Her non-protein and urea nitrogen were high and uric acid was normal. The serological findings were normal. The phthalein output was normal; alveolar carbon dioxide presented a normal level. The patient's observed and predicted weight agreed; there was some loss of lung volume. Earlier basal rates had shown definitely depressed values. The patient had been under intermittent thyroid medication and at the time of this test a not satisfactory observation was 12 per cent below prediction. The patient was both restless and nervous and the true basal rate was undoubtedly much lower. The blood pressure was low, the pulse normal, but the earlier records had shown a definite bradycardia. Her cardiogram was normal, as was a radiogram of the teeth; the audiogram showed some loss of hearing in both ears, most marked in the lower register; the eye findings were normal. The patient's sugar tolerance was midway between the normal and castrated level.

*Discussion:* The findings in this case were not entirely clear cut, as there was not full cooperation and the history of the earlier thy-

roid medication not entirely complete. That the patient had a surgical hypogonadism was established. Superimposed upon this there seemed to be an unquestioned thyroid failure of some degree of severity. As a thyroid failure may raise the sugar tolerance slightly, it was felt that the patient's value reflected the composite influence of both thyroid dysfunction and of the missing ovaries. We have learned indirectly that consistent thyroid medication has produced some betterment.

#### GROUP IV. THYROID DYSFUNCTION WITH HYPOGONADISM AND POSSIBLE PITUITARY DYSFUNCTION

CASE B-164. That this case is one of a pluriglandular involvement admits of no doubt. The degree and extent of such involvement, however, is in part uncertain. We hold no brief for the accuracy of the complete diagnosis. The patient when first seen was a woman of 40, complaining of nervousness, dyspnoea, choking sensations in the throat, headache, palpitation, loss of hair and occasional swelling in the left leg. Her difficulties apparently began some four years previously, when she became dyspnoeic following what she described as a "heat stroke." It was noted that she had been markedly fatigable prior to this. During her convalescence from the "heat stroke" she was hospitalized and a systolic blood pressure of 240 recorded. On her discharge she visited another hospital, where a diagnosis of thyrotoxicosis was made. A series of metabolism tests gave basal rates varying from +23 per cent to +8 per cent, the majority of them being well within the normal range. Operation followed the diagnosis and the left portion of the thyroid was removed. Prior to the operation the left leg had become sensitive to touch, and there was a burning sensation in it. All of her symptoms improved greatly after the operation, but in a few months they all returned with increased severity. A physician whom she consulted suggested further manipulation of the thyroid function by x-rays, but her previous surgeon advised strongly against any further thyroid interference. Her symptoms increased in severity and she consulted a new practitioner, who informed her that she had a cystic ovary, which he removed, at the same time ligating the thyroid artery. During this period (2 years) the patient was having very profuse menstrual periods at two months' intervals. Following her ovariectomy and thyroid ligation, she had regular periods for four months and then irregularity set in, with increased interval and very profuse flow. During her periods the thyroid region became swollen and a transitory skin eruption developed. She had diarrhoea also at these times. Her last operation left her in a worse condition than previously, and she was ultimately referred to this Clinic for study. With one ovary removed, a portion of the thyroid ablated and the thyroid artery ligated, she presented an interesting endocrine study. The family history was wholly irrelevant. The patient had the common childhood ailments and chronic intestinal disturbance from 17 to 30, which terminated in an intestinal obstruction, for which she was operated upon, with the removal of the appendix. She did not know if anything else were done at this time. The intestinal symptoms cleared up within a year of this operation. She had had a tonsillectomy and adenectomy 9 years before. During the thirteen years of her intestinal trouble she suffered from severe headaches. There was temporary relief after the operation, but they had returned with increasing intensity during the past few years. For many years the patient had been subject to severe epistaxis, her teeth had always been poor and soft, she had a palpitation all her life, and was highly

susceptible to respiratory infections. She had a tendency to constipation. The menses started at 14, the history of the interval having been given above. She had hay-fever every August. She had become considerably overweight, the excess being confined to the abdomen and hips. Physical examination showed a restless, poorly developed woman less than 4 ft. 11 in. tall and with a pronounced localized girdle obesity. The hair on the vertex was thin, the mouth showed an anatomical peculiarity with bilateral ridges under the tongue. There was a tenderness on deep palpation in the left lower quadrant. The left leg showed an enlarged calf with a hardened area, which the patient stated was associated with a venous thrombosis. She also stated that there had been a similar condition in the right leg. The remaining findings were normal. The urine volume was slightly high, elimination and balance good. All specimens showed albumin and, one, fine granular casts. The nitrogen partition was normal. The blood showed a slight lymphocytosis. There was no eosinophilia. Non-protein and urea nitrogen of the blood were above the normal level and the blood uric acid was 6 mgm., a value markedly above the normal. The serological tests gave no evidence of lues. The phthalein output was at the low borderline of the normal. The sugar tolerance was greatly depressed, the patient reacting positively with 10 grams, although no glycosuria had been recorded. The sitting height index was above 0.55. The patient was recorded as 22 per cent above prediction and actually was still more overweight. The lung capacity was 30 per cent below prediction. A urea curve showed a normal elimination. Alveolar carbon dioxide was below the normal. The patient's basal rate was within one or two per cent of prediction, but the recorded value was certainly somewhat high, as the patient was nervous. There were several tests, however, made independently, which were highly concordant. The pulse rate was somewhat rapid, the blood pressure showed the hypertensive level 190/110. The pelvic examination failed to demonstrate the adnexa. Radiographic findings of the skull, sella and sinuses were normal. There was no evidence of sub-sternal thyroid, and the heart and lungs were normal. The eye examination showed yellowish discs, enlarged blind spots, and a cutting of the form fields, more pronounced in the left eye and on the temporal side.

*Discussion:* This patient was seen a number of years ago, at a time when many of the more informative special examinations were not available. To summarize the endocrine status, she was a victim of partial, if not complete, gonad failure. Secondly, there was an earlier history of thyrotoxicosis which lacked support in the recorded basal tests, for which she had had both a partial removal of the gland and a ligation. That this might induce some degree of thyroid dysfunction would seem reasonable. A gonad operation would lower the basal rate somewhat. A compensatory residual hyperactivity of her thyroid remnant would raise it, but as it had brought it only to a normal level this thyroid influence could not have been a very marked one. The gonad failure could drop the sugar tolerance to 20 grams. A thyroid overactivity, to produce a further lowering, would probably be of considerable proportions, much more, at least, than those suggested by the basal rate. The patient was under 5 feet tall, she had a marked girdle obesity, an ample urine elimination, a very high blood uric acid, the significance of which is somewhat lessened by the slight increase recorded in the other nitrogen constituents of the blood; a lymphoid type of blood, a normal nitrogen partition, and low alveolar carbon dioxide, referable, presumably, to her gonad condition. On the basis of all these facts one could conceive of a pituitary disease which



had dated back to childhood. That she had a normal sella has no bearing on the matter, since many severe pituitary cases exhibit this condition. We are frankly in doubt as to the complete endocrine status of this case. Surgery has established the thyroid and in part the gonad condition; an initial and participating pituitary condition remains a matter of surmise. Our experience has led us to be very loath to place undue weight upon external appearances, but such observations as those of the eye examination and certain of the laboratory tests can be related to her known endocrinopathies with the greatest difficulty, if at all. With one ovary gone and the other possibly diseased, with a thyroid presumptively in a dysfunctional state, there still remain a group of objective findings that suggest even though they fail to define pituitary involvement.

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# THE VAGINAL SMEAR METHOD OF ASSAY OF THE OVARIAN HORMONE

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In a recent paper, Coward and Burn (1927) have expressed some doubt about the accuracy of the vaginal smear method (Allen and Doisy, 1923) of assay of the ovarian hormone. Their conclusion that the rat unit may vary as much as 1,000 per cent is so surprising that we have spent some time in developing more exactly some of the conditions which must be fulfilled to secure accurate assays. Prior to the appearance of the paper by Coward and Burn (1927) we had compared our assays with Laqueur and with a pharmaceutical house. In the first case we found 2.2, whereas Laqueur found 2.0 R. U. per 1 cc. In the second case, the commercial preparation was labeled 4 R. U. per 1 cc., but our result was 5 R. U. The remarkably good agreement with these samples and our other experiences with the routine assays of our preparations, had led us to believe that the vaginal smear method of assay is as reliable as other good procedures of assaying biological products. The data submitted in this paper seem to indicate that our faith was well founded.

Since it is important for the various laboratories (both chemical and pharmaceutical) interested in research on the ovarian hormone to be able to duplicate assays performed in other laboratories, we are giving in some detail the procedures that we have used.

## METHODS

*Animals:* All rats used were albinos reared from our own stock, which has not been augmented from outside sources for over two years. Our animals are fed an adequate diet containing yellow corn, carrots, lettuce, milk, raw beef, dog cakes and cod liver oil. Since Evans and Bishop (1922, also Evans 1928) have pointed out that on a diet deficient in Vitamin A the tendency on the part of the vaginal mucosa to form cornified epithe-

lial cells is no longer limited to the time of growth, maturation and rupture of the Graafian follicles, but is continuous even in ovariectomized females, an ample supply of cod liver oil was provided.

Vaginal smears of female rats weighing from 90-110 grams at an age of 7-8 weeks were made daily for a period of at least two weeks, to determine the regularity of the oestrous cycle. Only those animals having regular cycles were used. The ovariectomy was performed under deep ether anaesthesia, aseptic precautions being observed. In removing the ovary care was taken to remove the tube and the surrounding fat, in order that no remnant of ovarian tissue might be left to cause trouble in the later work. The animals recovered from the anaesthesia promptly, the incisions healed rapidly and very few infections resulted from the operations. Daily vaginal smears were made for two weeks following ovariectomy, to determine whether all ovarian tissue had been removed. Negative smears were obtained in every case, indicating that the ovariectomy had been complete.

*Injections:* In our earlier work we attempted to simulate the ovarian activity by injecting preparations of the hormone in three portions given at four-hour intervals. This repetition of injection, of course, entails more work than a single injection, but our early experiments seemed to indicate that more uniform results were obtainable in this way. Laqueur (1927), Zondek (1926), and possibly others, have gone to the other extreme and administered six injections distributed over two or more days. While it seems to be true that a smaller quantity so supplied will produce the typical cornified cells, this procedure seems to possess little advantage over the injection in three portions, and, of course, has the disadvantage of requiring more work. As will be brought out in the discussion of our experimental work, animals receiving three injections respond uniformly enough to give satisfactory routine assays. It is important for workers to adopt a uniform number of injections, as the actual weight of the rat unit diminishes as the number of injections increases.

Some of our experiments seem to indicate that the extent of genital atrophy influences the amount of hormone required to produce a positive smear. We have, therefore, practiced what we term *priming*. Our test animals are used once a week, thus corresponding roughly to the length of the normal ovarian cycle

(4-5 days). In the event that an insufficient quantity of hormone is administered and a negative result obtained, the rat is *primed* the following week by the injection of a known extract containing 1.5 R. U. The following week the rat is again ready for use. It occasionally happens in our preliminary rough assays that the priming is omitted until a rat has two successive negative reactions, but in final accurate assays one negative reaction is cause for a priming injection.

Injections are always made subcutaneously. In agreement with Evans and Burr (1926), we have found that the results of intraperitoneal injections are less uniform.

*Preparations Used:* The preparations used, which had been previously standardized, were an aqueous solution, No. 15578, and two oil solutions, No. 30540 and No. 34072. We are indebted to the Digestive Ferments Company for the former and to E. R. Squibb & Son for the latter two.

*Explanation of Symbols:* Each smear spread over an area of 1 sq. cm. is stained and examined thoroughly with low power. The results of the vaginal smears are expressed by means of the following symbols:

- + nothing but cornified cells.
- ± ± ± predominance of cornified cells, but a few nucleated epithelial cells; no leucocytes.
- ± ± cornified cells, nucleated epithelial cells and a *very few* leucocytes. The cornified and nucleated epithelial cells predominate; in fact, the number of leucocytes is so small that they may be overlooked unless a thorough examination of the entire smear is made.
- ± leucocytes, nucleated epithelial cells and some cornified cells.
- mainly leucocytes.

Though there has been considerable discussion (Laqueur, 1926; Loewe, 1926; Zondek and Ascheim, 1926) upon the estimation of activity from the smears, we have adopted the view that a predominance of cornified cells, with some nucleated epithelial cells and a *very few* leucocytes, should be taken as a positive reaction. Frequently a test animal is encountered which responds in this way to, for example, 0.25 cc., and on subsequent injection

of 0.40 cc. of the same preparation gives the same type of smear. We believe that the results of assaying will be more uniform by evaluating this reaction as positive, even though this smear is not the typical full oestrous smear of the normal female.

The smear ratings, +,  $\pm\pm\pm$ , and  $\pm\pm$  are taken to mean that the response is positive and that at least 1 R. U. has been injected. The  $\pm$  means that a partial response to an insufficient dosage has occurred, but in our judgment it should be classed as only little better than the —. In the discussion, the +,  $\pm\pm\pm$ , and  $\pm\pm$  of our tables are grouped under the positive or + designation, while the  $\pm$  and — are classed together as negative, or —.

#### RESULTS

Ovariectomized rats from No. 345 to No. 397, inclusive, were used in this study of the limitations of the vaginal smear method of assay. Twenty-five animals were injected with 0.27 cc. and 0.15 cc. of preparation No. 15578. From the results of a few preliminary tests it was found that 0.21 cc. contained 1 R. U. The two dosages given then contained 30 per cent more and 30 per cent less than 1 R. U.

Of the 25 animals injected with 0.15 cc., two gave a positive reaction; in fact, one of them (No. 359) gave a + response on three different trials. However, both of these animals failed to respond positively to 0.10 cc.

With the larger volume (0.27 cc.) all animals except No. 358 gave a + reaction. This rat furthermore gave a — reaction to 0.34 cc., but on another trial gave a + reaction. In two out of three trials No. 369 gave a negative response to 0.27 cc., but responded favorably to 0.34 cc.

Of this series of animals, a total of four, or 16 per cent, responded irregularly. The two worst offenders, No. 359 and No. 369, were discarded and not used for subsequent tests.

Eleven rats were used in the next series of experiments in which an oil solution was injected. Ten of the eleven animals gave a negative smear upon the injection of 0.18 cc. The response to a slightly larger quantity, 0.24 cc., in eight animals was +. Owing to an insufficient quantity of this preparation, the other three were injected with an approximately equal

quantity of another extract. Two of the three gave a positive reaction. Of this series, then, 2 of the 11 rats differed appreciably in their response. This is not surprising, since the smaller dosage was only 25 per cent less than the larger.

The third series is more extensive in that a greater range of dosage was employed. Of the 24 rats studied, 7 had been used in the second series. The irregularity previously exhibited by No. 378 and No. 380 is not apparent in the third series.

With the smaller volume, 0.15 cc. or 0.17 cc., 3 of the 24 animals gave a + reaction. Each of these gave a negative response upon repetition of this volume. When the dosage was increased to 0.25 cc., 12 of 23 animals gave a — reaction. In 8 animals of the 23 this volume was injected again, and in each case the former response was obtained.

Obviously, from the equal distribution of — and + reactions, 0.25 cc. could not be regarded as 1 R. U. The dosage was increased to 0.30 cc. in certain rats, including those that had given a — reaction to 0.25 cc. Of the 15 receiving the larger quantity, 11 gave a + reaction. Two of the other 4 on subsequent trial gave a + reaction with 0.30 cc., while 1 of the others gave a + reaction with 0.40 cc.; but the fourth gave a — reaction and required 0.50 cc. to show the typical cornified cells. It would be advisable to discard rats as irregular as the last two mentioned.

It seems, then, from these series of experiments, that in spite of our precautions to secure uniformity, about 20 per cent of the animals will be somewhat irregular in their response to injections of the ovarian hormone. By the injection of a standard stock solution, those rats which respond too easily or with too much difficulty may be eliminated. In effect, a standardization of the rats is carried out before they are used for routine standardization of unknown preparations. We have been following this procedure for some time. Notwithstanding this precaution, it is probably better to adopt Laqueur's (1927) idea that the volume which suffices to produce a + reaction in 75 per cent of the animals be regarded as 1 unit. For rough work a few animals suffice, but for more accurate assays it is advisable to use a considerable number in arriving at the final unitage.

*Period of Serviceability of Test Animals:* After using 19 of the test rats for weekly tests for a three months' period, they were again injected with 0.27 cc. of preparation No. 15578. Though these animals had increased considerably in weight, all gave a positive reaction; in fact, 14 gave + and 5 the  $\pm\pm\pm$ . Two months later, *i. e.*, five months after spaying, 5 animals were tested with 0.27 cc. and 0.15 cc. With the first dosage all were +, with the latter all were —.

Table II contains the results of tests conducted after six and seven months' use of some of the test animals employed in obtaining the data of Table I. Of the 22 rats used, all gave a positive response to 0.27 cc., and 19 of the 22 gave at least the  $\pm\pm$  to 0.15 cc. Of the three that were negative, one, No. 397, had required approximately 2 R. U. six months earlier, before a positive smear was obtained.

The interpretation to be placed upon Table II is that after prolonged use for testing, the animals become more sensitive and respond to smaller doses. Such a condition would, of course, introduce irregularities which increase the difficulty and decrease the accuracy of the assays. Our evidence, though limited in amount, indicates that the animals do not show an increase in sensitivity during the first five months of use. To be on the safe side, it might be well to use the animals only four months, *i. e.*, for 16 to 18 weekly tests.

*Regeneration:* The regeneration of ovarian tissue to which attention has been called by Davenport (1925) and Parkes, Fielding and Brambell (1927) might be a source of annoyance and uncertainty in assaying ovarian preparations. Parkes and his coworkers found that regeneration occurred in only 11 out of 121 ovariectomized mice, but Davenport found a larger proportion in a series of animals in which the capsules and tubes were not removed.

As already stated, we have removed the ovaries with the periovarial fat, the fallopian tube and part of the uterus. In a series of 30 of the rats used in obtaining the data of Table I, and then subsequently for routine assays for a period of 5 or 6 months, no ovarian tissue was found at autopsy. Furthermore, though daily vaginal examinations were made, no oestrus or pro-oestrous smears were detected, except those at the normal time interval, after the injection of an active extract. During the





two weeks prior to autopsy, vaginal smears were made daily, but in this period no injections were made. Two smears were obtained which had an unusual number of epithelial cells for a dioestrous period. Dr. W. D. Collier of the Pathology Department kindly made a detailed histological examination of the region of the ovary, but was unable to detect any ovarian tissue.

Though the number of animals included in this study is somewhat limited, it seems safe to conclude that regeneration of ovarian tissue is not common in rats. In our experience during the past five years, the occurrence of oestrous or pro-oestrous smears at unexpected times has been very rare. It is improbable, then, that regeneration can cause much trouble in assay work, if the rats have been carefully ovariectomized.

#### PROPOSALS REGARDING TECHNIC OF STANDARDIZATION

1. Make daily smears for a two or three weeks' period before ovariectomy. Only those animals with normal cycles should be used.

TABLE II

#### RESPONSE OF TEST ANIMALS AFTER A PROLONGED PERIOD OF USE

Rat No.	Volume Injected Results of Tests		Rat No.	Volume Injected Results of Tests	
	0.15 cc.	0.27 cc.		0.15 cc.	0.27 cc.
354	+	+	389	± ±	+
358	± ±	+	390	± ±	+
360	± ±	+	391	± ±	+
363	± ± ±	+	392	± ±	+
364	+	+	393	± ±	+
381	± ±	+	394	—	± ±
382	+	+	395	± ±	+
383	+	+	396	+	+
384	+	± ± ±	397	—	+
385	± ±	+			
386	± ± ±	+			
387	+	+			
388	± ±	± ±			
After 6 months use			After 7 months use		

2. Make daily smears for two weeks after operation but before the beginning of injections. Discard any animal showing oestrous or pro-oestrous smears later than the second day after operation.

3. Prime the animals with 2 R. U.

4. One week later test the reaction of each animal by the injection of 1.3 R. U. If the smears are negative, discard the animal.

5. A week later test the reaction to 0.70 R. U.; if positive smears occur, discard the animal.

6. Use each animal for no longer than four months.

7. In attempting accurate assays, prime all animals by injecting 1.5 R. U., if the reaction of the preceding week was negative.

8. Use a sufficient number of animals. If 75 per cent of the animals injected with the same volume give a + reaction, consider that the amount injected contained 1 R. U.

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# THE DISTRIBUTION OF THE OVARIAN HORMONE BETWEEN LIQUOR FOLLICULI AND THE RESIDUAL TISSUE\*

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Although the work of Allen and Doisy and their collaborators has emphasized the importance of the Graafian follicle in the production of the oestrous hormone, no clear data regarding the amount of hormone that can be extracted from the liquor folliculi and the residual tissue have been published. To be sure, the results of a few random tests (Doisy, Ralls, Allen and Johnston, 1924,) have been cited, but no systematic report has been made. The English investigators (Dickens, Dodds, and Wright, 1925; Parkes and Bellerby, 1926,) have studied the distribution of the hormone between the follicular fluid and the residual tissue, and have published figures which indicate a more or less uniform distribution. They have concluded that the importance of the follicle has been unduly emphasized. To ascertain whether their position or the view expressed by Allen and Doisy is correct, we have undertaken the extraction of ten samples of liquor folliculi and the residual tissue from which the juice was obtained.

Fresh ovaries from the morning slaughtering were obtained from the chill room of the packing plant about 11:00 a. m. They were selected in that only those with apparently normal, ripe follicles were used. The liquor was aspirated from the ripe follicles and from others of size sufficient to contain appreciable quantities of liquor folliculi. The fluid was preserved with two volumes of 95 per cent alcohol, while the residual tissue was rinsed with water, passed through a meat chopper and mixed with twice its weight of alcohol.

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The extraction of the liquor folliculi was carried out as described by Ralls, Jordan and Doisy (1926), but the purification with petroleum ether was omitted. The residual tissue was extracted by the procedure used in earlier work from this laboratory (Doisy, Ralls, Allen and Johnston, 1924). Care was taken to avoid the destructive effects of peroxides in the solvents used. Aliquots of the final extracts were distilled and the residue taken up in olive oil for the injections.

#### DISCUSSION

Data from the extraction of ten consecutive samples of liquor folliculi and residual tissue are available for discussion. An examination of Table I shows that the concentration of ovarian hormone in the liquor folliculi is much greater than in the residual tissue. It is significant that our results are in accord with the earlier work of Doisy and his associates (1924), but are contrary to the findings of Dickens, Dodds, and Wright (1925) and Parkes and Bellerby (1926). The English investigators, however, state that the follicles from which the fluid was obtained were not always large, since ovaries were seldom obtained from animals in oestrus. Doisy, Ralls, Allen and Johnston (1924) obtained between 220 to 2,000 rat units per kgm. of pig liquor from large follicles, with the average value falling about 450. (In a later work the average of 12 preparations was about 900 R. U.) Less than 200 units per kgm. were obtained from ovaries from which the liquor folliculi had been removed. These earlier findings are in agreement with our results. We obtained 690 to 1,228 rat units per kgm. of hog liquor, with the average value of 933, in contrast to the corresponding residual tissue, which gave from 124 to 199 rat units per kgm, with the average value of 167.

If one chooses to neglect the conception of concentration and merely considers the content of hormone in the two fractions of the ovary, our figures show almost twice as much in the liquor folliculi as in the residual tissue. The average for the 10 experiments are 304 and 187 rat units respectively. It must, of course, be realized that these figures are not absolute because of the impossibility of removing all of the follicular tissue. Many small follicles present in the ovaries were not aspirated, and con-

sequently contributed an uncertain amount of hormone to the residual tissue fraction. Zondek (1926) has found by his implantation procedure that the follicle wall contains sufficient hormone to produce oestrous in the spayed mouse. This quota of hormone would also appear in the residual tissue yield in our work. Considering both sources of error, it seems probable that our data for the residual tissue may be considerably too high and the figures for the liquor folliculi correspondingly low.

One experiment was carried out with cow ovaries. The corpora lutea were carefully dissected out, the liquor folliculi aspirated and the residual tissue treated by the same procedure used with the hog ovaries. The rat units per kgm. of tissue were: Corpora lutea 8, residual tissue 99, and liquor folliculi 613. These results do not agree with the findings of Parkes and Bellerby (1926), who state that the liquor folliculi from cow ovaries contains more hormone than the liquor folliculi from the hog. However, upon another point our findings are in accord with theirs, in that the amount of hormone of the residual tissue of hog ovaries is almost double that of cow ovaries. These data may be correlated with the fact that it is impossible to remove all the liquor folliculi from hog ovaries because a large number of small follicles are distributed throughout the ovary, whereas cow ovaries generally have only a few large follicles, since as a rule but one follicle ripens at each oestrous.

There seem to be two possible explanations of the differences of our results from those of Parkes and Bellerby. 1. The ovaries used by the English investigators may have been mainly in the dioestrous stage, and therefore, according to our view, contained only a small quantity of the hormone. The ovaries used in our work were carefully selected and only those with large, normal follicles used. Approximately one-fourth of the weight of the ovaries was liquor folliculi. 2. The method of extraction may possibly have caused the low yields obtained by Parkes and Bellerby. In a recent paper (Thayer, Jordan and Doisy, 1928,) we have shown that peroxides present in ethyl ether may produce serious losses of activity of the ovarian hormone, and that the more refined a preparation is the more readily oxidation occurs. The liquor folliculi extracts are much purer than extracts of the residual tissue, and therefore may suffer greater losses.

## SUMMARY

1. The observations of ten experiments support the view of the importance of the Graafian follicle in the production of the oestrous hormone.

2. The average number of rat units per kilogram from liquor folliculi is 933 and from residual tissue 167.

TABLE I

COMPARISON OF LIQUOR FOLLICULI AND RESIDUAL TISSUE

Preparation No.	Residual Tissue			Liquor Folliculi		
	Weight	Total Yield	Yield per Kilo	Weight	Total Yield	Yield per Kilo
	Grams	Rat Units	Rat Units	Grams	Rat Units	Rat Units
3A	2264	323	112	517	130	830
7A	1057	211	198	312	312	998
8A	1031	206	199	309	309	988
9A	854	106	121	262	218	830
10A	789	112	141	321	203	690
11A	1019	139	132	352	293	820
12A	1276	255	198	365	455	1228
13A	1092	156	112	317	317	982
14A	907	181	199	265	265	980
15A	922	181	198	210	240	984
Average...	1124	187	167	326	301	933

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# THE THYROID GLAND IN INFECTIONS; THE EFFECT UPON THE BASAL METABOLIC RATE\*

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The fact that the thyroid gland plays a very important role in the growth of an animal and in the regulation of the body metabolism has been recognized for some time. In a recent communication (1) we called attention to the fact that in cer-



Fig. 1. Section from the thyroid gland of a dog dying of intestinal obstruction. The normal architecture of the gland has been changed by the desquamation, hyperplasia and loss of colloid. The remnants of a few acini may still be seen.

\*Read before the Twelfth Annual Meeting of the Association for the Study of Internal Secretions, Minneapolis, June 12, 1928.

tain systemic infections and in severe toxemias very definite chemical as well as histological changes in the thyroid gland could be demonstrated. These changes varied considerably with the severity of the infection. Microscopically we were able to show that in the more virulent infections there was desquamation and death of many of the acinous cells, loss of colloid and hyperplasia of many of the remaining cells. This resulted in a marked change in the normal architecture of the gland (Fig. 1). There was a concomitant enlargement of the gland. Upon chemical analysis, however, the iodine content per gram of tissue was found to be about half the amount found in the thyroid glands of the control animals.

Such facts are not surprising when one considers the important part the thyroid plays in the metabolism of the body. It has long been an established fact that in infections there is an increase in metabolism. More recently calorimetric studies of the increase in heat production have been made by Barr and Du Bois in malaria (2), Coleman and Du Bois in typhoid fever (3) and McCann and Barr in tuberculosis (4). Likewise it has been found by Schick, Cohen and Beck (5) that during convalescence after pneumonia the basal metabolic rate is often lower than normal. They found this true in other diseases associated with a low pulse rate during convalescence (6): During the febrile stage of an infection a definite relationship between the rise in fever and the rise in metabolism has been noted by Du Bois (7) which conforms roughly to the law of physical chemistry first suggested by Van't Hoff, i.e.: "With a rise in temperature of 10 degrees, Centigrade, the velocity of chemical reactions increases between two and three times" (8). This relationship, however, is subject to some variation probably depending to a certain extent upon the differences in the level of protein metabolism maintained in different diseases.

With these facts in mind we have studied the effects of experimentally produced infections in animals on the basal metabolism and the changes produced following the administration of iodine. We have also noted definite changes in the clinical course of these infections as well as in the chemical and histological structure of the thyroid gland.



## METHOD

The apparatus used for the determination of the basal metabolism consisted of a closed respiratory chamber of the Benedict type to which a specially devised mask was attached. This mask was made of a small can to which was attached a rubber sleeve that fit snugly over the dog's muzzle. If a rubber dam bandage was first wrapped around the dog's head at the level of the eyes it was found that this apparatus was perfectly airtight and apparently comfortable. Encircling the fingers around the rubber sleeve at the dog's muzzle is strongly advised to prevent leakage at this point. The dogs used in these experiments were kept on a standard diet consisting for a large part of cooked meat, care being taken to avoid any food that might contain iodine. Before the experiment was begun a small amount of thyroid tissue was removed for microscopic examination, not enough, however, to be a factor in producing subsequent hyperplasia of the gland. After recovery from the biopsy the animals were trained to lie perfectly quiet and relaxed on a table while the metabolism tests were being run. This seemingly difficult part of the procedure was accomplished with surprising ease. Usually after five or six attempts the animal would remain quiet throughout the entire test and uniform readings could be obtained.

A real difficulty, however, was encountered in the computation of the surface area. The generally used Du Bois height-weight formula was naturally inapplicable. Because of the marked variation in shape any surface area formula based on the weight alone is inaccurate when applied to dogs. It would seem, however, that the important fact is the determination of the normal metabolic level of the particular animal under experimentation rather than using a standard factor. Kunde and Steinhaus (9), by using dogs of comparatively the same weight, obtained an average basal metabolism for normal dogs of 771.2 calories per square meter per 24 hours. Meeh's formula was used in their work. Boothby and Sandiford (10) quote a somewhat higher average. The surface area formula used by us was  $0.103\sqrt[3]{wt^2}$ . As might be expected, there was considerable variation in those dogs of extreme weights. Our average for

19 normal dogs was 885.21 calories per square meter per 24 hours.

In these experiments 19 dogs were used. Of this number 7 were fed iodine in the form of Lugol's solution, 2 were fed thyroid extract and 10 were used as controls. The Lugol's solution was masked in the food; the dose used was one minim per kgm. of body weight. The iodine feedings were begun several days before the infections were produced and continued through-

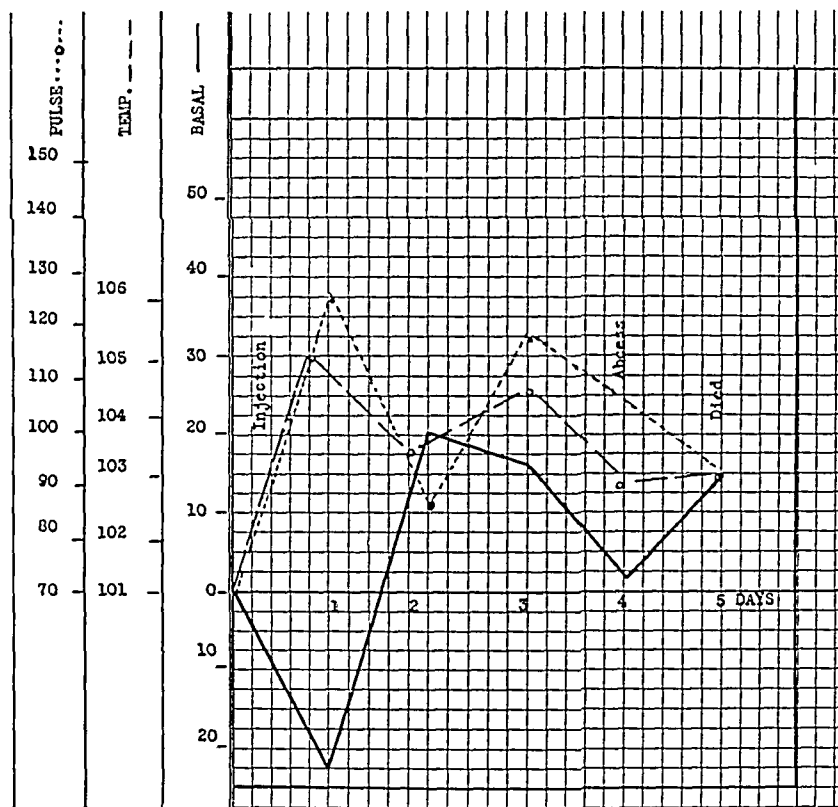


Chart 1 Basal metabolism, pulse and temperature of a dog that died 5 days after the injection of 0.8 cc. of toxin per kgm. of body weight. Note the initial drop in metabolism below normal. The subsequent rise is not as great as is usually seen, suggesting a depression of oxygen consumption. The pulse rate is unusually high.

out the experiment. A few infections were produced by ligation of the appendix. The majority, however, were produced by the injection of a toxin consisting of the contents of a strangulated loop of gut. Upon culture it was found also to contain Hemolytic Streptococcus, B. Welchii, B. Coli, and B. Proteus.

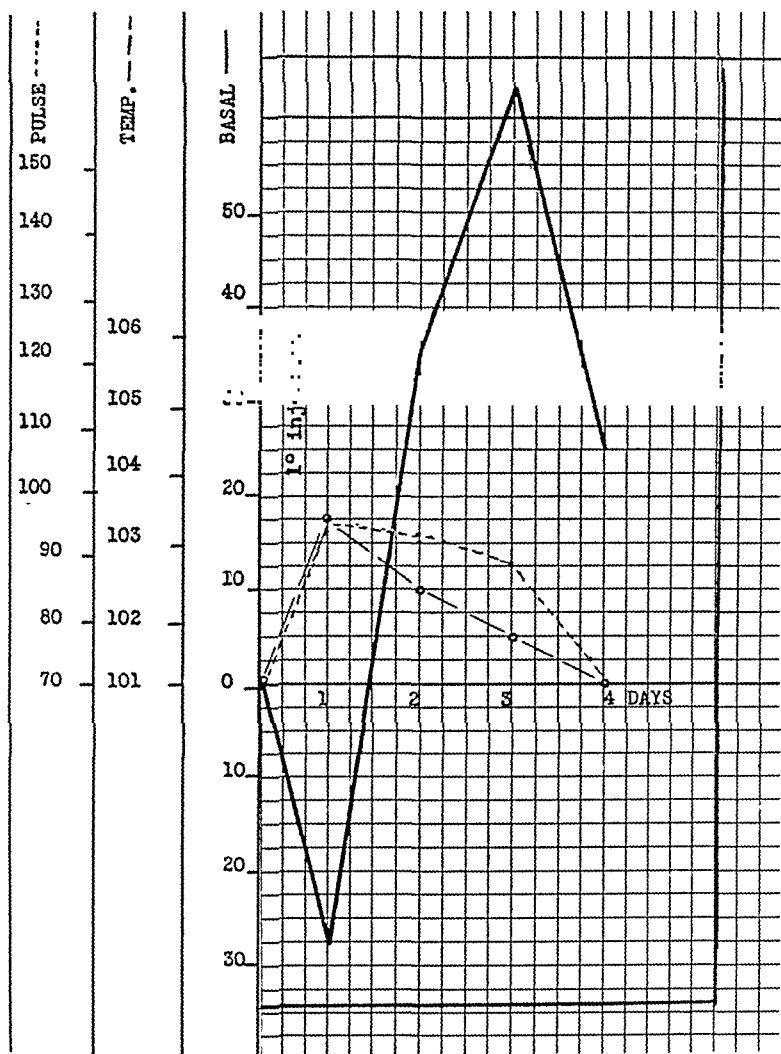


Chart 2. This chart shows the initial depression in metabolism following the injection of toxin with a subsequent high rise. This animal was not fed iodine.

The amount used was eight-tenths of a cubic centimeter per kgm. of body weight and both control animal and the animal that had been fed iodine were injected at the same time in order to avoid any daily variation in the strength of the toxin.

As soon as several consistently low basal metabolism readings had been obtained the animals were injected with the toxin

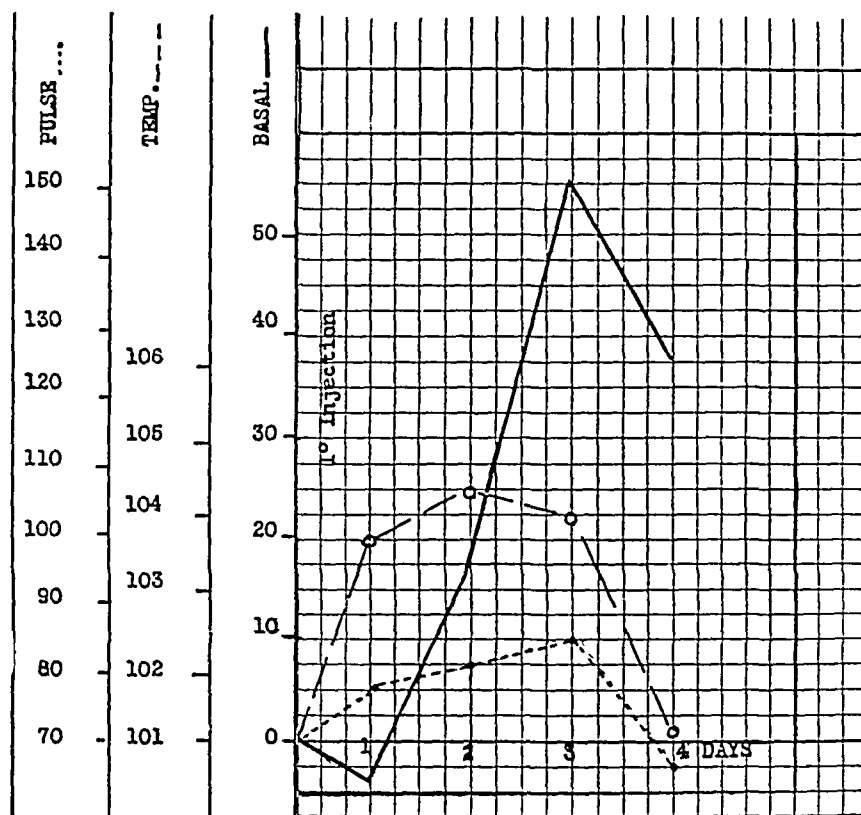


Chart 3. This dog received iodine before and during his infection. Note the absence of the depression phase and the failure of the basal metabolism to rise subsequently as high as in the control dog shown in Chart 2.

subcutaneously with comparatively little discomfort. Daily basal metabolism readings were then made until the animals died or began to recover from their infections. Those animals that recovered were then given larger doses to determine if there was any variation in the resistance of those that had been fed iodine and the control dogs.

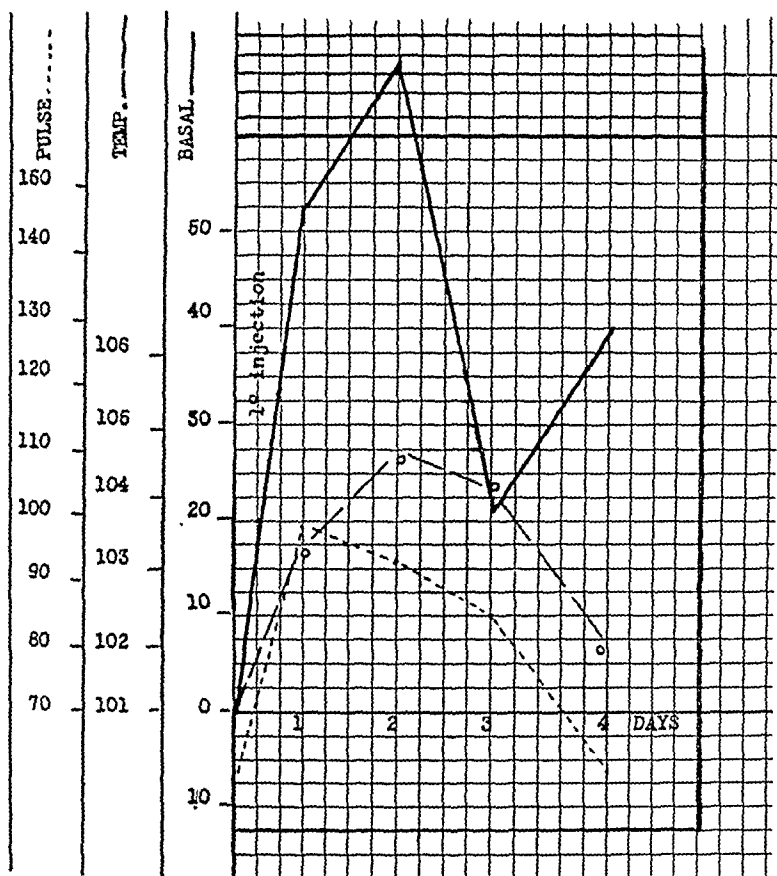


Chart 4. Control dog—without iodine. Note the lack of initial depression, with high immediate rise in metabolism. This animal was not as sick as those shown in Charts 1 and 2. See Fig. 2 for the microscopic picture of the gland in this dog.

## DISCUSSION

If the infection was so fulminant in character that the animal died within twenty-four to thirty-six hours there was noted a drop in oxygen consumption below normal which persisted. If, however, the infection was not quite so severe, there was seen an initial drop in basal metabolism below normal which

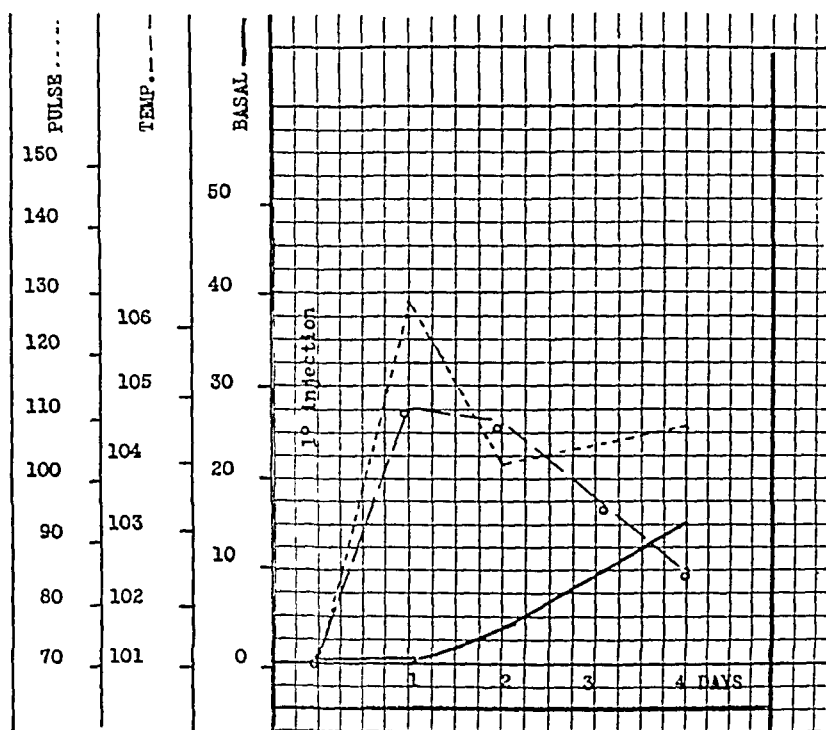


Chart 5. The basal metabolism curve of dog fed iodine during the experiment. Note the comparatively slight rise in basal metabolism. Compare with control animal shown in Chart 1. Section from the thyroid of this dog is seen in Fig. 3.

soon rose to well above normal where it persisted until the animal recovered (Charts 1 and 2). In still less severe infection the initial drop was not seen, the basal metabolism rising to well above normal but not as high as in the preceding group of cases (Charts 4, 6 and 8).

In those animals that were fed iodine the basal metabolism was consistently lower than in the control cases with the exception of the very severe cases in which the control dogs showed

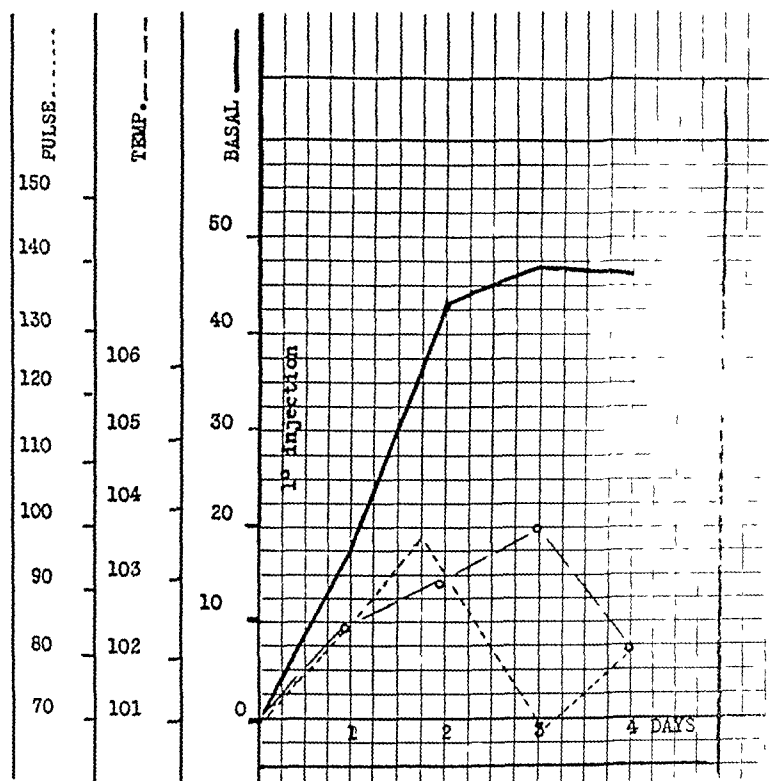


Chart 6. Basal metabolism of dog not fed iodine. Compare with Chart 7

a depression of oxygen consumption. Here the readings were higher (Charts 3, 5, 7 and 9). In general the temperature and pulse rate were perhaps lower in the iodine dogs but not as low as one would expect when considering the very marked effect on the pulse rate in exophthalmic goiters. Practically all of the dogs that were fed iodine showed clinical improvement before the control dogs. Neither was the immediate reaction so

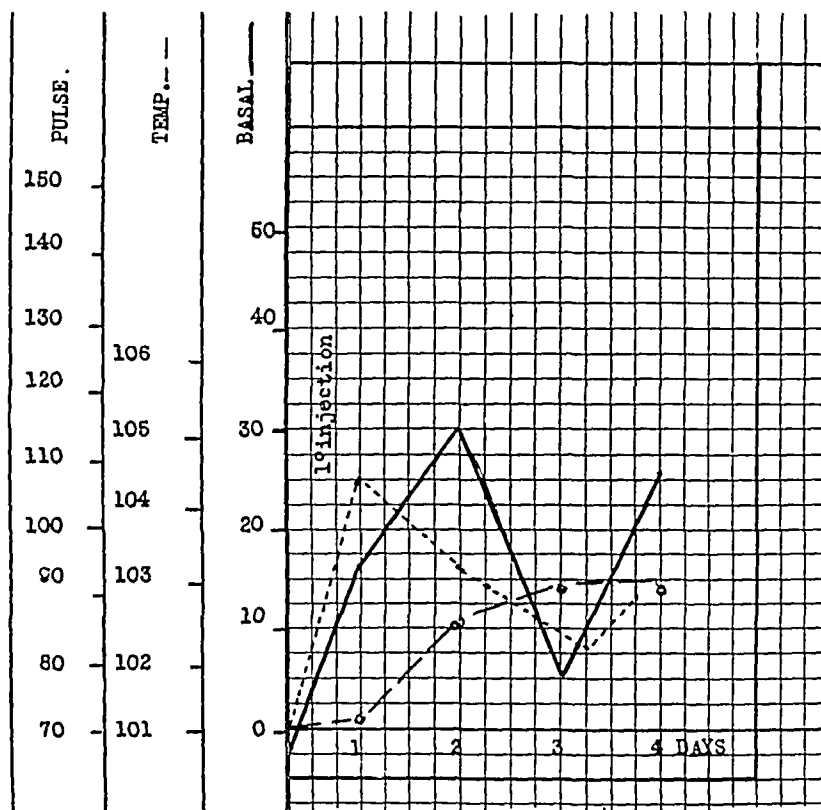


Chart 7. Basal metabolism of dog fed iodine during the experiment. Compare the lowered oxygen consumption with the control animal shown in Chart 6.

severe. None of the iodine dogs died following the injections, while two of the control dogs died. Following ligation of the appendix one control dog, one dog that had been fed iodine and one dog that had received thyroid extract died. These latter two animals lived over fifty hours, while the control animal lived about thirty hours.



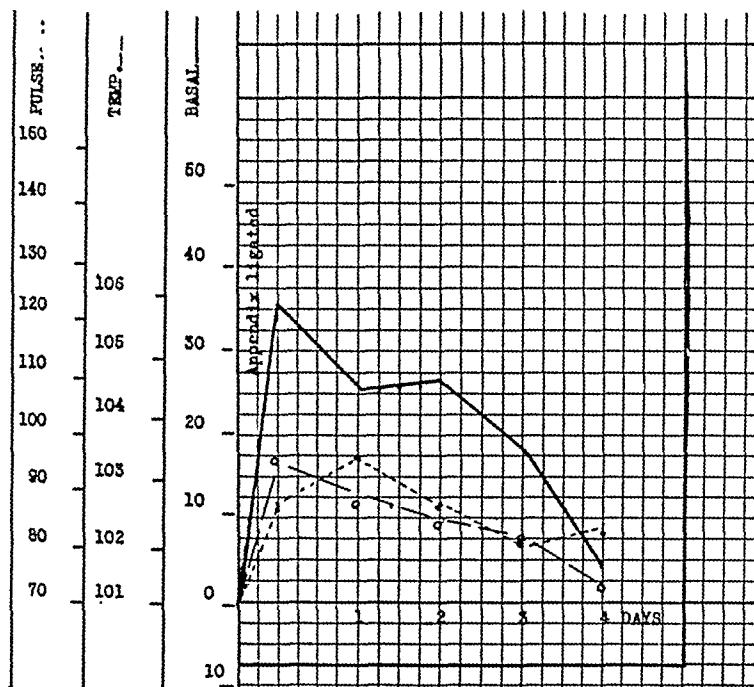


Chart 8. Reaction following the ligation of the appendix in a dog not fed iodine.

Histologically the hyperplasia and desquamation so often seen in the thyroid gland of animals with severe infections were absent in those glands that had received iodine (Figs. 2 and 3). Likewise the latter group of glands often contained as much as two or three times the amount of iodine seen in the normal thyroid of a dog. The dogs receiving thyroid extract showed similar changes to those dogs receiving iodine but not quite so marked.

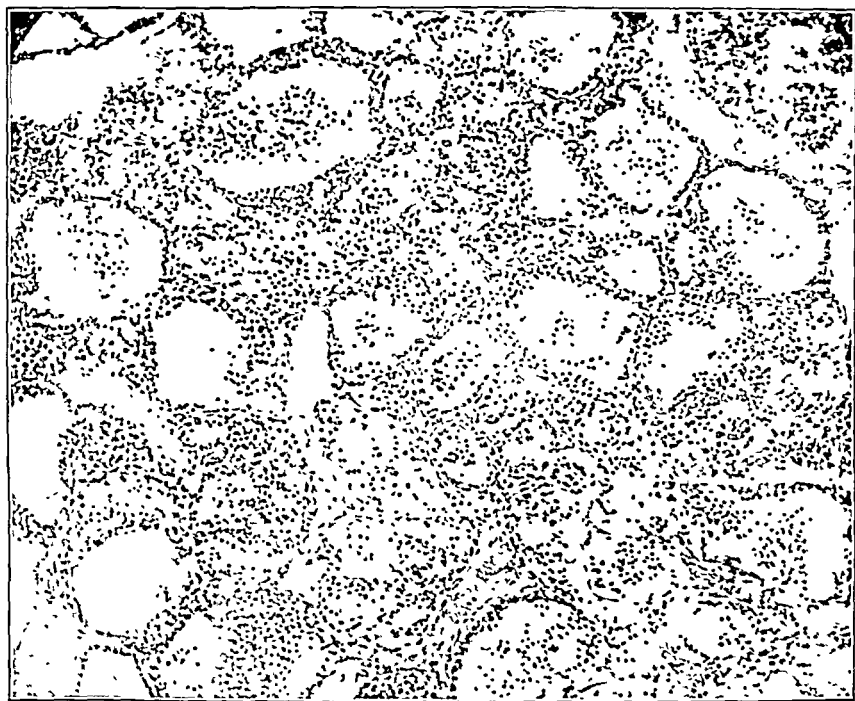


Fig. 2. Section from the thyroid of a dog following the injection of toxic material as described in the text. The basal metabolism curve is shown in Chart IV. Here one sees desquamation, deficiency of colloid and beginning of hyperplasia. Many of the cells are columnar in type.

That such changes as described above cannot be explained on the basis of hyperpyrexia alone can be shown by the fact that similar changes in the metabolic rate and structural and chemical changes in the thyroid gland may be produced by the injection of a toxin such as histamine without the production of fever (Chart 10, Fig. 4).

As Farrant (11) has shown, certain organisms are more prone to produce the structural changes in the thyroid gland than others. It is probable that infections produced by such organisms are those that are associated with a high level of protein katabolism. Those conditions such as chronic tuberculosis (4) and chronic bacterial endocarditis, in which protein metabolism is relatively low, produce a relatively lower rise in basal metabolism and show considerably less structural change

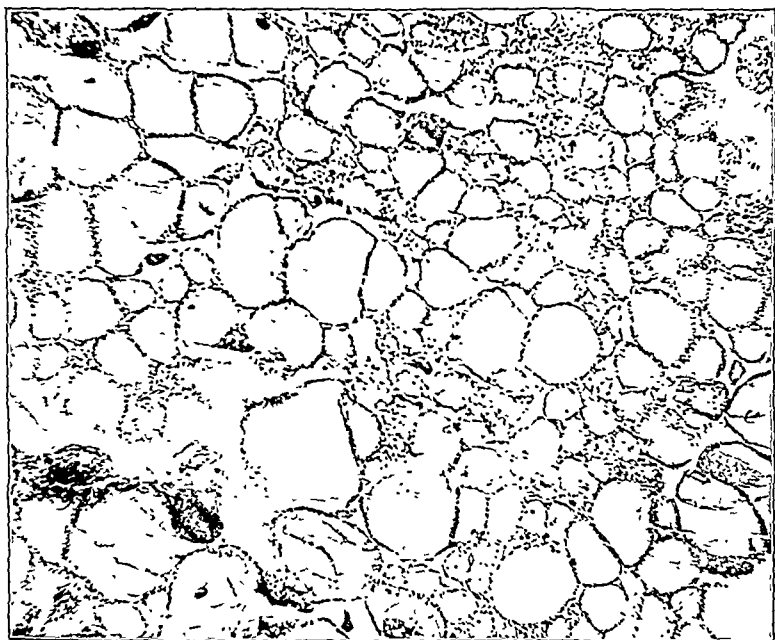


Fig. 3. Section from the thyroid of a dog, the basal metabolism curve of which is shown in Chart V. This animal was injected with toxin, but received iodine before and during the experiment. Note the practically normal appearance of the gland. Compare with Fig. 2, the control animal for this experiment. This gland contained several times the normal amount of iodine, while that shown in Fig. 2 contained much less than is found in the normal gland.

in the thyroid gland. Generalized peritonitis on the contrary produced extensive changes in the thyroid gland (12).

Usually there is no great change in the respiratory quotient during infections, suggesting a fairly normal fat and carbohydrate metabolism. The idea that we are dealing chiefly with the effects of protein metabolism is strengthened when we consider that heat production is increased through the specific dy-

namic action of proteins. That this specific dynamic action could be produced by the feeding of component amino acids has been shown by Lusk (13), and more recently by Wilhelmj and Bollman (14) by intravenous injections of certain amino acids. We have been able to produce similar changes in the thyroid gland to those described above by the repeated injections of large amounts of glycocholl subcutaneously sufficient to cause

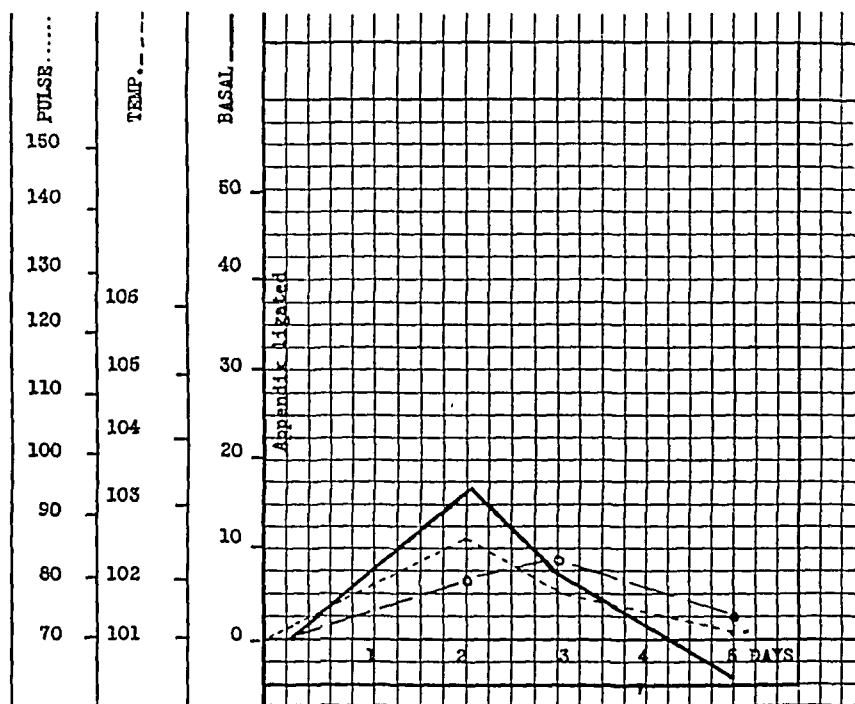


Chart 9. Reaction following the ligation of the appendix in a dog fed iodine. Note the reduction in the basal metabolic level. Compare with Chart 8, the control.

death (Fig. 5). It has been shown (14) that this amino acid has a fairly high specific dynamic action. That the thyroid may be involved in the specific dynamic action of proteins is not a new idea. Baumann and Hunt (15) have demonstrated that there is a gradual disappearance of this phenomenon following the complete removal of the thyroids of rabbits. Incomplete thyroidectomy showed only a decrease in the specific dynamic

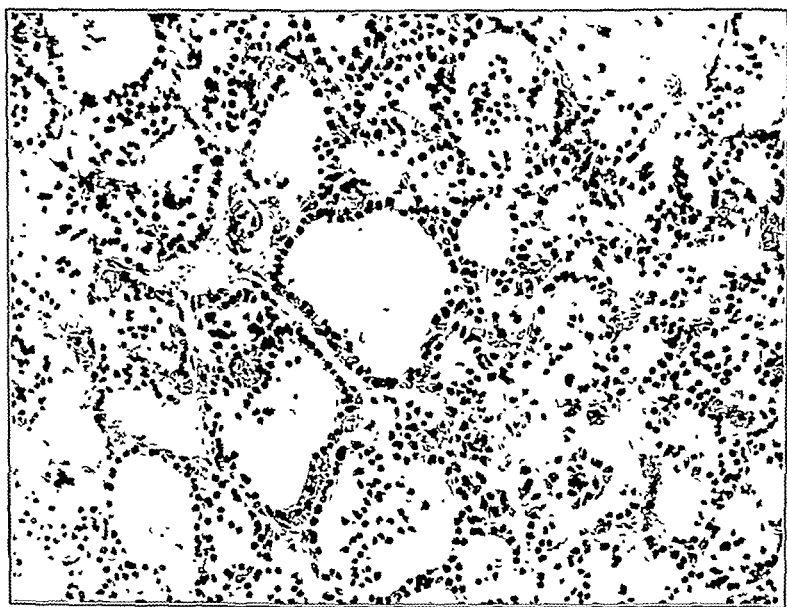


Fig. 4. Changes in the gland of an animal that received subcutaneous injections of histamine. Note the same changes as seen in Fig. 2. See Chart X.

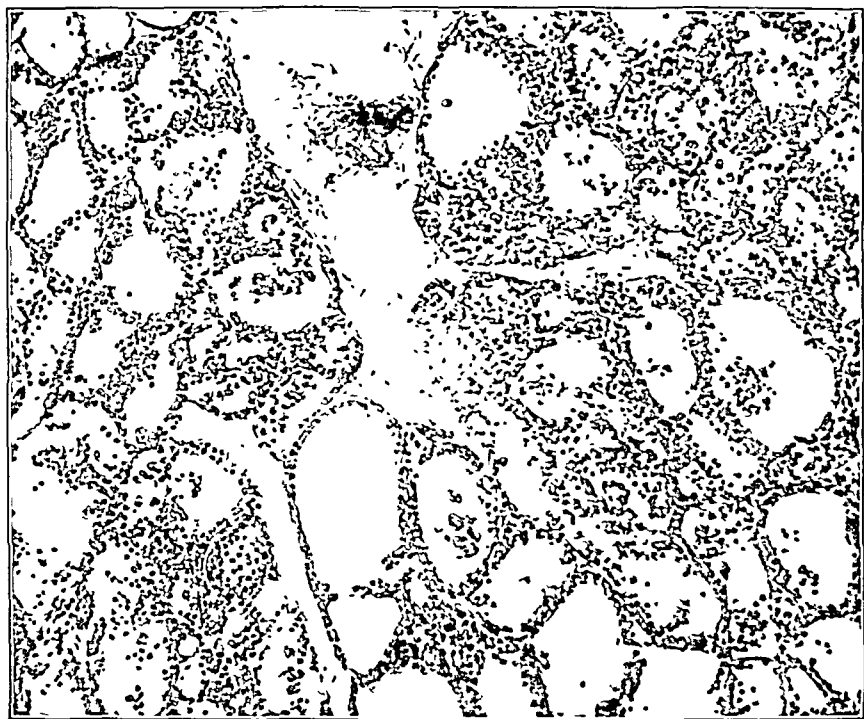


Fig. 5. Changes in the thyroid gland of a dog which was given glycocoll subcutaneously. This animal was given 1 gram per kgm. of body weight on the first day, 2 grams on the second day, and 2.5 grams on the third day. The changes here resemble those seen in Fig. 4.

action that could be returned to normal by the administration of potassium iodide.

The mechanism by which these changes are produced is not easily explained. It could possibly be a direct toxic action on the thyroid parenchyma. If this were true one would expect to find a similar destruction in other parenchymatous organs.

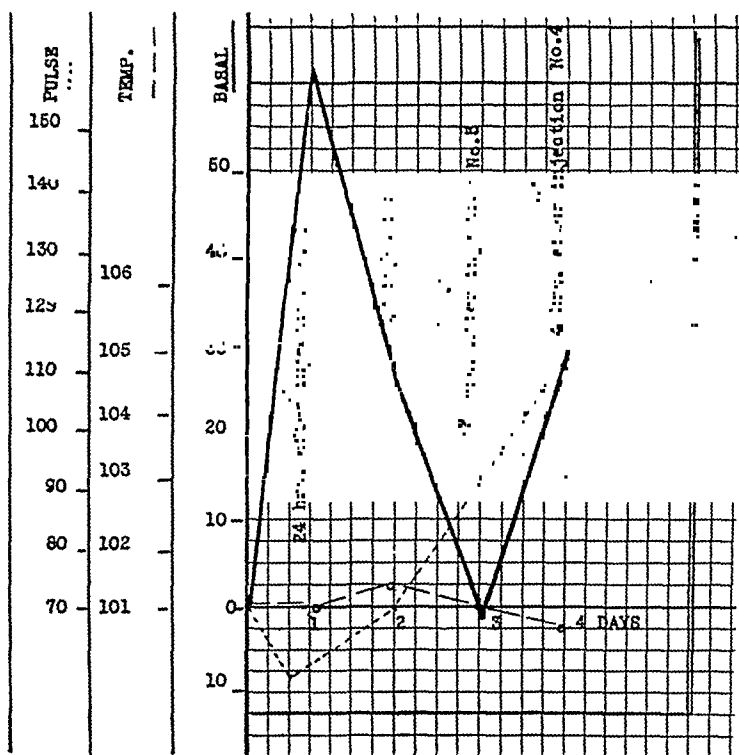


Chart 10. Basal metabolic curve, pulse and temperature of dog following the injection of histamine. Dog sacrificed on the 5th day. There is practically no rise in temperature. The metabolism is at its highest 24 hours after injection. The 2nd reading, taken 36 hours after the first injection and just before 2nd injection, shows a beginning fall. The third reading, taken 2 hours after the 3d injection, shows no rise. This may possibly be interpreted as a depression in oxygen consumption immediately following the injection of histamine. The 4th injection shows a beginning rise. See Fig. 4.

With the exception of a moderate amount of cloudy swelling and chronic passive congestion this was not noted. Furthermore, such a direct toxic action would not sufficiently explain the depletion of thyroid iodine. Hyperplasia, loss of colloid

and even death of the acinous cells could be explained by stimulation of the thyroid gland even to the point of exhaustion by demand of the somatic cells upon the thyroid for its catalytic secretion. It is an interesting fact that the feeding of iodine during such periods of strain lowers the basal metabolism and produces an entirely different picture in the structure of the thyroid gland.

### SUMMARY

Characteristic microscopic and chemical changes have been produced in the thyroid glands of dogs by the experimental production of infections and toxemias. These changes have been associated with a rise in basal metabolism.

The feeding of iodine has tended to prevent the above changes and lower the basal metabolism.

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# PINEAL AND METAMORPHOSIS THE INFLUENCE OF PINEAL FEEDING UPON THE RATE OF METAMORPHOSIS IN FROGS

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Before taking up the discussion of the effect of pineal feeding on amphibians, it might be well to summarize the effect of pineal feeding on higher animals, as reported by different observers. Very little has been done in this field.

## RESULTS OBTAINED FROM FEEDING OF PINEAL GLANDS

Dana and Berkeley (1913) find that feeding results in increased general growth development of genital organs and deposit of sub-cutaneous fat above normal in young guinea pigs, rabbits, and kittens.

McCord (1914-15) finds accelerated growth in chicks guinea pigs and puppies. Injections of pineal extract with guinea pigs showed increased rate of growth. McCord states that veal pineal has more marked effect than that of old cattle. Dogs fed pineal gland were one month ahead in mental development. Guinea pigs developed rapidly and bore young 14 days ahead of controls. Chickens fed on pineal from old cattle showed slow growth which was greatly accelerated by shifting them to veal pineal. McCord concludes that if pineal from young animals is fed in small amounts to young animals the body growth will be stimulated till normal growth is attained with only a moderate amount of precocity of mental and sexual development.

McCord (1915) further says that children mentally defective when treated with pineal extract do not show any acceleration of growth but do show mental improvement if treated before 15 years of age. The digestive juices of the stomach and intestine sometimes change the composition of gland extract.

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\*Aided by the G. W. Carnrick Company.

Intravenous pineal injections have shown, however, that pineal extract is not decomposed in the digestive process since the result in both cases has been the same.

Very little has been accomplished in the feeding of pineal to amphibians. The following is a brief summary of the findings in this field:

Adler (1914) in feeding tadpoles had 19 alive at end of 19 days. Three lived 82 days. No abnormality in sexual development was noted. None developed into frogs.

McCord and Allen (1917) find that beef pineal extracted with acetone if fed for 10 days causes transparency of tadpoles 45 minutes after feeding on account of contractions of the melanophores or pigment spots of the lower layer of the epidermis. This acetone extract does not greatly influence growth. Its residue, however, does, thus showing that there are two active principles in the pineal.

McCord (1917) finds that tadpoles fed for two weeks on pineal tissue are twice the size of controls and show no signs of differentiation. He finds that the ultimate differentiation is earlier, but that metamorphosis occurred in the controls also.

In reviewing the above data relative to the feeding of pineal to both amphibians and other vertebrates the following questions arise:

1. Will feeding of the gland to amphibians accelerate the rate of growth as in the case of higher animals?
2. Will deposits of fat result as in the case of higher animals?
3. Will there be an increase in size of the pineal fed individuals?
4. How do results obtained from pineal feeding compare with those obtained by thyroid feeding?
5. What other results are noted in connection with this experiment?

#### EXPERIMENTAL PROCEDURE

It was with these questions in mind that we began the experiment of feeding tadpoles pineal extract in connection with pork liver. In carrying out this work 54 tadpoles of *Bufo americana* were used. Feeding began on June 16, 1928 and ended on July 20, 1928. The animals were fed once each week as much liver as they could consume at one time and the remainder was removed in order to prevent poisoning by decay.

The pineal was in desiccated capsule form ( $\frac{1}{2}$  grain pineal with  $\frac{1}{2}$  grain milk sugar) and was not mixed with the food at all but was simply placed in the water of the battery jars where the tadpoles were kept. Twelve hours after giving the pineal the water was changed as it would become slightly tinged with a translucent colloid substance and the tadpoles showed an abnormal disposition to remain motionless at the surface if the water was not changed.

Marked changes were noted in the appearance of the pineal fed individuals as early as a week after the first feeding. A clear, baglike membrane developed on the ventral side just anterior the pelvic region. The bulging ventral portion of the abdomen (which is characteristic of normal tadpoles) disappeared and the ventral surface became flattened. The dark pigmentation of the sides and tail disappeared, due no doubt as McCord states, to contractions of the melanophores. Except for some white, flaky granular material, the skin in these regions was almost transparent. The entire body outline became slimmer and more salamander-like in appearance than that of the controls. A sluggish condition for two days following each pineal feeding was noted. The controls on the other hand played and swam about in the lively manner of all normal tadpoles.

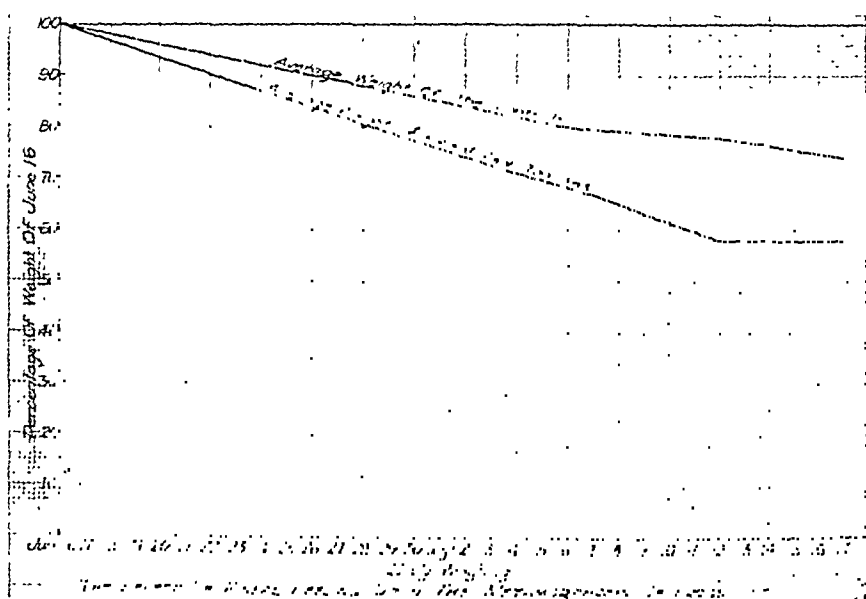
The rate of metamorphosis proceeded rapidly after the second feeding of pineal (July 1) as is shown in the record of development of the fore legs. Rapid absorption of the tail followed and many deaths resulted at that stage before final absorption of the tail. (The action of pineal at this point was similar to that of thyroid). It was also noted that death invariably resulted if individuals at the stage of development of the fore legs were given pineal. It soon became apparent that the dose of  $\frac{1}{2}$  grain pineal was too severe and as the death rate continued at these two stages of development, no pineal was given at all between the dates of July 1 and July 12.

The results of such discontinuance were almost immediate. No further deaths resulted and on July 11 one tadpole passed safely through the dangerous stage of tail absorption, became a frog and fed on insects. Two other tadpoles developed into frogs on the following day (July 12) and also fed on insects.

By July 13 it appeared that the effects of the pineal administered two weeks previously had run its course. No more

tadpoles developed fore legs. They regained the dark normal pigmentation of the sides and tail and the abdomen became pouched and rounded more like that of the controls. The body volume also appeared to increase. It was clear that the effect of pineal—unlike that of thyroid—was on the wane and if discontinued entirely development would proceed along the same lines as that of the controls.

Accordingly, it was decided to give a dose of only  $\frac{1}{4}$  grain pineal and attempt to start up development again. This was done on July 13 and the results were almost immediate, as is shown in the table of the development of fore legs. Three of the five that developed fore legs on July 15 died and two died on July 17 upon developing fore legs, thus showing that pineal, even in small doses, is very dangerous at this stage. The remainder of those fed on pineal again resumed the pale, washed-out appearance and the abdomen became flattened again as before.



Contrary to the findings of Dana and Berkeley with mammals the feeding of pineal to amphibians results in a rapid loss of body weight. As has been said before, this is apparent to the eye of the casual observer. The average weights given below of

both pineal fed individuals and controls show that an enormous tearing down of body tissue results from pineal feeding.

### AVERAGE WEIGHT OF TADPOLES

<i>Date</i>	<i>Pineal Fed</i>	<i>Controls</i>
June 16.....	2.674 grams.	2.674 grams.
July 6.....	1.817 grams.	2.14 grams.
July 12.....	1.54 grams.	2.075 grams.
July 17.....	1.55 grams.	1.98 grams.

The accompanying graph (see previous page) also affords a comparison in percentages as to the relative loss in weight in the controls and feeders.

The rate at which pineal hastens the development of fore legs may be seen by the following table:

#### II. Rate of Foreleg Development of Pineal Feeders.

(Pineal fed from June 16 to July 1 once each week.)

<i>Date</i>		
July 1	1	No pineal fed from July 1 to July 12.
5	1	
6	2	
8	2	
9	2	
10	1	Effects of pineal disappearing here. One-fourth grain pineal given on July 13. Note immediate effect of resumption of pineal dosage
11	2	
12	0	
13	0	
14	0	
15	5	
16	3	
17	2	

### SUMMARY

1. Pineal hastens the rate of metamorphosis, much in the same manner as thyroid does, but is not so powerful as thyroid in this respect. Furthermore, if the feeding of the pineal is discontinued, development slows up. Resumption of pineal feeding results in a sudden speeding up of the rate of metamorphosis.

2. Unlike the findings of McCord (1917) the pineal fed individuals lost weight rapidly while the weight of the controls more nearly remained constant.
3. Twenty-two pineal fed individuals developed fore legs and eight passed through the tail absorption stage into that of the adult form in the course of thirty-one days. No change whatever in the way of differentiation was noted in the controls.

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# A NOTE ON THE RELATION OF LIGHT TO THE ACTION OF PARATHYROID EXTRACT

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MONTEVIDEO

From the work of Hanson; Berman; Collip; Clark and Scott; Hjort, Robinson and Fendrick; Fisher and Lawson, the effect of acid extracts of parathyroid glands on the blood calcium is now well known. A rise in the blood calcium level above 17 mgm. per 100 cc. is dangerous to the life of the animal (according to Collip's and Salvesen's studies) leading to a sequence of symptoms of more or less gravity (diarrhea, etc.). If administration of the extract is continued the symptoms become more and more grave simultaneously with the augmentation of the calcemia.

Collip and Scott have observed that it is possible to induce a rapid rise of the blood calcium by injections of small quantities of the extract once or twice every day. Collip succeeded in some cases in making the calcium rise with 2 or 3 injections of 20 units each and to maintain it elevated for some time.

In our laboratory, aided by Dr. Bennatti and Miss E. Balet, we have confirmed the earlier work, using Parathormone (Lilly) and noting hypercalcemia, grave symptoms and, in continued experiments, death. Blood calcium was determined by the Tisdall-Kramer method as modified by Scott, centrifuging the fluid. The dogs on which we experimented weighed between 7 and 12 kgm. It is especially to be noted that during the experiments the dogs were kept in a dark cellar. The diet was invariably meat, milk, bread and water. But in these animals we observed that to be able to make the calcemia reach the higher levels, as rapidly as did Collip and others, we had to repeat the injections many times over a period of 8 to 10 days. The hypercalcemia thus secured decreased rapidly as soon as the injections were discontinued. The following table sets forth the details of one of our experiments:

Dog—8 kgm. normal.

December 6—Blood calcium.....	0.0105
December 6—Injected 20 units extract	
December 7—20 + 20 units extract	
December 8—20 + 20 units extract	
December 8—Blood calcium.....	0.0132
December 9—20 + units extract	
December 10—20 units extract	
December 10—Blood calcium.....	0.0165
December 10—20 units extract	
December 11—20 + units extract	
December 12—20 + 20 units extract	
December 13—20 units extract	
December 13—Blood calcium.....	0.0177
December 14—None injected	
December 15—20 units extract	
December 15—Blood calcium.....	0.0150
December 16—20 units extract	
December 16—Blood calcium.....	0.0108
December 17—Normal.	

At first these meager results were attributed to lack of potency in the extract employed. But wishing to take a photograph of one of the animals on which we experimented, during the period of grave symptoms, we took the animal from the dark cellar to the laboratory, where he was for some time exposed to sunlight before a window. We observed, then, that his symptoms became rapidly more grave (more dyspnea and asthenia). When the same phenomena were noted in case of a second animal, we decided to investigate specifically the effect of light on the reactions.

A normal, white fox terrier dog, weighing 9 kgm., had blood calcium of 0.0098. He was kept in darkness throughout the experiment. He was given parathyroid extract subcutaneously in 20 unit doses, according to the following schedule:

December 5—20 units	
December 6—20 units	
December 7—20 units, blood calcium.....	0.0128
December 8—20 + 20 units	
December 9—20 + units	
December 10—20 units, blood calcium.....	0.0143
December 10—20 units	
December 11—20 + 20 units	
December 12—20 units, blood calcium.....	0.0150

At 4:30 p. m. the blood calcium was determined (0.0150). The animal was asthenic and dyspneic. He was then brought to the laboratory and exposed to sunlight for 45 minutes. His dyspnea and asthenia increased considerably and at 5:15 p. m. the blood calcium was 0.0157. He died during the night.



How much weight is to be ascribed to the 5 per cent increase in the blood calcium in this single case is, of course, doubtful, but the direction of the change upon exposure to light is certainly of interest. It would seem to correlate with the augmentation of calcium provoked by exposure to ultra violet light in case of rachitic and parathyroprivic subjects.

Further experiments of this nature have been prevented by lack of extract.

That sunlight has no influence upon the blood calcium of normal animals nor of non-treated parathyroprivic animals with hypocalcemia and tetany we have shown experimentally. Two characteristic cases may be cited.

A normal dog, weighing 9.500 kgm., was parathyroidectomized on March 3rd. The blood calcium at this time was 0.0097. On March 5th the animal was tetanic and the calcium had fallen to 0.0058. After exposure to sunlight for one hour the symptoms did not change and the blood calcium remained at 0.0056. Death occurred the following day.

A normal dog, weighing 8 kgm., was kept in darkness for 8 days. The initial calcium level was 0.0102. After exposure to the sun's rays for an hour he showed dyspnea. The calcium level was 0.0100.

It was concluded, then, that the specific influence of the sun's rays is shown in dogs treated with parathyroid extracts.

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# A CASE OF DIABETES, REFRACTORY TO INSULIN, WITH HYPERPLASTIC AND ADENOMATOUS ADRENALS

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There is probably no part of the field of morbid anatomy in which the pathologist is more greatly vexed than in the pathology and correlated physiology of the endocrines. There are available a large number of papers dealing with the physiology, chemistry and pharmacology of the ductless glands, yet we are far from a proper evaluation of the role of these organs in the entire body economy. Again, there are many papers dealing with the pathology of this or that organ in correlation with certain clinical signs or even a disease entity. It is easy to say that destruction of the adrenals is correlated with Addison's disease, yet many obstacles must be hurdled before such a statement is accepted as absolute. What about the 15 per cent of cases of clinical Addison's disease that present no destruction of the adrenals demonstrable at autopsy? Why is an extract of the adrenals of little value in the treatment of the disease? Turning to the thyroid, the pathologist speaks of colloid goitres, parenchymatous goitres and adenomata of the thyroid, while the clinician speaks of thyrotoxicosis, Basedow's disease and other terms which mean little to the pathologists. Each is apparently oblivious of the existence of the other.

Even as complicated as the physiologic pathology of the one endocrine may appear, undoubtedly there are diseases, or at least symptoms resulting from a combined disease of two or more endocrines, a pluriglandular disease. These may be the result of a general systemic disease affecting two endocrine organs, or there may be two independent processes, either of which may influence to advantage or disadvantage the functional derangement of the other.

Despite the known "thin ice" upon which one is treading in correlating pluriglandular pathology with disturbance of func-

tion of the endocrines, I venture to record a possible pluriglandular complex as an explanation of a case recently seen on the autopsy service of Starling-Loving Hospital, at Columbus.

**CASE REPORT.** M. G., white, female, 34 years of age, was admitted to Starling-Loving Hospital (Case No. 261560) on March 30, 1926, in a state of coma. From subsequent questioning the following history was elicited:

**Family History:** The mother died at 45 of unknown cause. The whereabouts of the father is unknown. One brother and one sister are living and well. One brother died in infancy.

**Past History:** During childhood the patient had measles, pertussis, mumps, diphtheria and chicken pox. She suffered a mild attack of influenza in 1918.

**Present Illness:** In September, 1924 (19 months ago) the patient states that she first noticed fainting spells when she got up in the morning. She also complained of marked polyuria, frequency and nocturia. She was treated on a low carbohydrate diet, until January, 1925, when insulin was started, the dose being 9 units three times a day. In July, 1925, in Washington, D. C., she suffered from what was apparently an attack of diabetic coma, remaining unconscious for 24 hours. The present attack began the same day she entered the hospital.

**Physical Examination** at the time of admission is essentially uninformative. Her blood sugar was 560 mgm. per 100 cc. Urinalysis showed: sp. g., 1.032; acid; albumin, trace; sugar, 5.8 per cent; no casts; acetone and diacetic acid present. A blood examination showed hemoglobin, 82 per cent; red blood corpuscles, 4,606,000; white blood corpuscles, 12,680; polymorphonuclear leucocytes, 92 per cent. The Wassermann reaction was negative.

**Course:** Under insulin and glucose therapy the patient made a good recovery from the coma. By the next morning the blood sugar was down to 80 mgm., the urine was acetone-free and the patient fully conscious and feeling fine. Toward noon of this same day she presented symptoms of returning coma and a blood sugar determination revealed 510 mgm. per 100 cc. On insulin and glucose she was brought back to normal, clinically and according to laboratory tests. During the succeeding four days the progress was rather stormy, with alternate periods of semi-coma with a markedly fluctuating blood sugar. While apparently on a rigorous diet and insulin therapy, carefully controlled, on the morning of April 5th the patient again passed into coma. A blood sugar determination at 8:00 a. m. revealed 1075 mgm. glucose per 100 cc. Twenty-five units of insulin apparently had a slight effect. There was a distinct acetone odor to the breath and an abundance of acetone and diacetic acid in the urine. At 10:00 a. m. the blood sugar was 169 mgm. per 100 cc. The patient died at 10:12 a. m., April 5, 1926.

An *autopsy* was performed on April 6, 1926, at the Starling-Loving Hospital, by Dr. Ernest Scott and Robert A. Moore.

The body was that of a rather large, mannish type woman.

The stomach and intestines were somewhat distended with gas. The omentum was normal. The appendix was apparently normal. The peritoneum was smooth. There was no fluid in the peritoneal cavity. The liver was at the costal margin, pale in color and of a slightly yellowish and somewhat mottled appearance. The gall bladder was small and contained no calculi. The spleen was normal in size. In the thoracic cavity there were adhesions over the upper lobe on the right side. There was no increased fluid in either pleura. The left lung was free, and there were areas of consolidation. The pericardial sac was normal.

*Organs of the Abdominal Cavity:* The pancreas was rather thin, flat and somewhat flabby in its structure. The glandular tissue was somewhat reduced in amount. No areas of fibrosis or other focal or diffuse pathologic changes were noted. The spleen was normal in size and color. On section, the pulp substance was solid and paler than normal. The left adrenal gland was thickened with apparently very great increase in cortical substance. This increased substance was of yellowish color. On section, the adrenal gland showed a diffuse adenomatous growth measuring 1 by 1 cm. in the cortex. The left kidney was of usual size; the markings were very distinctly retained. The cortex was of usual thickness, measuring 6 mm. The right kidney was similar to the left. The adrenal gland on the right side was also large and contained a distinct adenomatous nodule measuring  $1\frac{1}{2}$  by 1 cm. The uterus contained an early menstrual flow in the endometrium; otherwise it was normal. The right ovary was cystic. The urinary bladder showed a purulent cystitis, but was otherwise normal. The liver was slightly enlarged; the cut surface was pale, rather yellowish and mottled.

*Organs of Thoracic Cavity:* Careful examination of the lungs, heart and mediastinum failed to reveal any active pathologic change. There were a few scars at the right apex and a calcified nodule in the center of the upper lobe. The thyroid was not unusual.

*The Head:* Examination of the meninges and brain showed no abnormalities. The pituitary gland was apparently normal.

*Microscopic Examination:* Thorough microscopic examination of the pancreas demonstrated that the majority of the islands of Langerhans were structurally normal. A few islands showed atrophy, hyaline degeneration and fibrosis. There was no other associated abnormality in the acini, interstitial tissue, ducts or blood vessels of the pancreas. The adenomatous nodules in the adrenals presented the typical appearance of adrenal cortex, with nothing to distinguish them microscopically as tumors. The remainder of the organs presented microscopically no abnormalities.

*Anatomic Diagnosis:* Hyaline degeneration and fibrosis of the islands of Langerhans, cortical adenomata of the adrenals, and purulent cystitis.

#### SUMMARY

The case is reported of a woman of 34 who died in diabetic

coma despite very large doses of insulin. The blood sugar shortly before death was 769 mgm. per 100 cc. At autopsy the pancreas was found to be normal except for atrophy of a small proportion of the islands of Langerhans and slight reduction in the amount of glandular tissue. The only other endocrine abnormality found was an adenomatous and hyperplastic pair of adrenal glands.

I am indebted to Dr. G. I. Nelson for the clinical history of this case.

# OVARIAN AND PLACENTAL HORMONE EFFECTS IN NORMAL, IMMATURE ALBINO RATS

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## INTRODUCTION

This experiment was planned to study the effects of active extracts of the ovary and placenta in normal, immature male and female albino rats.

Much has been written in recent years on the effects of injections of these hormones into the rabbit, mouse and rat, both in mature and immature animals. Little attention, however, seems to have been paid to recovery after injections are discontinued. There also remains some disagreement as to antimasculine effects of these hormones, as will be brought out in the discussion of the literature. Consequently the present paper seeks to establish definite hormone effects and then to follow through the period of recovery in several animals.

## LITERATURE

In a recent paper Allen and Doisy (1927) presented an extensive review of the experimental work thus far accomplished on ovarian and placental hormones. The work to date on this subject has demonstrated that there is a casual relationship between the internal secretion of the ovaries and the oestrous cycle in female animals and the menstrual cycle in the primates. Injections of ovarian follicular hormone into spayed animals, normal animals during inactive periods, and pregnant and lactating animals were found to produce oestrous changes with the characteristic reactions of the genital system. Later it was discovered that placental extracts produce the same results as the ovarian follicular hormone when injected into female animals.

The effects of ovarian and placental hormones on the female genital organs seem to be well established, but the effects on the testes and male genital organs are not so well agreed upon.

Herman and Stein (1920) reported that injections of extracts of corpus luteum into young male rats and rabbits delayed the attainment of sexual maturity and that prolonged injections of larger quantities of the corpus luteum extract in adult rats and rabbits led to degenerative changes in the testes. Fellner (1921) also found degeneration of the testes produced by injections of lipoid extracts of placenta or of corpus luteum. Bugbee and Simond (1926) reported the absence of antimasculine effects from injections of follicular hormone, while Laqueur (1926), with a highly purified extract, menformon, found definite antimasculine effects. Therefore, the question as to the effect of this hormone on the male genital organs is still to be finally decided.

#### PROCEDURE

In this experiment normal young albino rats of two separate litters were used. The first litter consisted of three females and six males. Of these one male and one female were used as controls and the others used as test animals. In the second litter there were four females and seven males. Of these one female and two males were used as controls and the others as test animals. This made a total of five controls and fifteen test animals. Injections were begun simultaneously in all the animals when the first litter was eighteen days old and the second litter twelve days old. Follicular hormone (Squibb) was injected into the test animals and an equal amount of Ringer's solution into the controls. Injections were made twice daily, at approximately eight o'clock in the morning and five o'clock in the afternoon. The younger rats were started with 0.2 cc. injections of extract which contained five rat units per cc. The potency of this extract was standardized by tests in spayed mature female rats. The older rats were given 0.25 cc. of the same extract. Therefore, the animals were receiving respectively two and two and one-half rat units each day. This procedure was continued for eight days. Weights of the rats were recorded daily at five o'clock and observations noted as to the condition of the vagina and position of the testes. On the ninth day after the beginning of injections and each day following, injections were increased in amount so that there was an addition of 0.25 rat units each day.

After fourteen days, due to a shortage of Squibb's extract, "Estrogen" (Parke, Davis Co.), diluted to five rat units per cc., was substituted. The same daily increase of 0.25 rat units was continued and weights and observations recorded. After twenty-two days of continual injections the two male controls of the younger animals were sacrificed together with three injected males of the same litter. These animals had received a total of 7½ rat units in twenty-two days, as shown in the following tables.

TABLE I  
Males

Rat	Treatment	No. Days Injected	No. Rat Units Injected
MN <sub>1</sub> Ra	Control	Ringer's	0
MN <sub>2</sub> Na*	Injected	35	21½
MN <sub>3</sub> Ra	Injected	24	12½
MSBa	Injected	24	12½
MN <sub>4</sub> La	Injected	24	12½
M <sub>5</sub> Na*	Injected	24	12½
MNNB	Control	Ringer's	0
MSREB	Control	Ringer's	0
MNRB	Injected	20	7½
MNLAB	Injected	20	7½
MNLB*	Injected	36	192
M <sub>2</sub> NB	Injected	25	102

\*All animals were killed immediately after the last injection of extracts, with the exception of animals MN<sub>2</sub>Na, M<sub>5</sub>Na, MNLB, which were observed for 14, 11, 13, and 11 days, respectively, during the period of recovery from effects of the hormone.

TABLE II

Rat	Treatment	Body Weights		No. of Days Injected	No. R. U. Injected	Vagina Opened	Wt. of Thymus Grams
		At Start Grams	At Death Grams				
FN <sub>1</sub> La	Control	21.0	78.5	Ringer's	0	Closed	.223
FN <sub>2</sub> Na*	Injected	18.0	90.0	24	124	After 9 days	.147
FN <sub>3</sub> Ra	Injected	18.0	71.1	24	124	After 9 days	.163
FN <sub>4</sub> Nb	Control	15.0	62.3	Ringer's	0	Closed	.203
FN <sub>5</sub> Rb	Injected	13.5	61.5	24	101	After 13 days	.180
FSLEb*	Injected	10.0	58.8	25	102	No record	.161
FSHBb	Injected	12.0	69.2	36	192	After 14 days	.171

\*All animals were killed after the last injection of extract, with the exception of animals FN<sub>2</sub>Na and FSLEb, which were observed for 12 days during the period of return to normal.

§Estrogen, Parke, Davis & Company's preparation. The writer wishes to acknowledge the assistance of both E. R. Squibb & Sons and Parke, Davis & Co. for considerable supplies of active extracts.



Weights were taken of the entire body, genital organs and thymus. These tissues were then fixed in Bouin's fluid together with the other endocrine glands and prepared for histological study. The following week a number of the other animals were sacrificed. All this time the increase in amounts of injections of 0.25 rat units per day was continued in the other animals. These animals had received 124 rat units in twenty-four days, as shown in the above tables. This left only four of the younger rats, of which two were males and two females, and three of the older animals, of which one was a female and two were males, all of which had been continually injected. From this point on there were no increases in the amount of injections because of the excessive doses the animals were already getting. Of the younger four, one male and one female were kept alive without further injections while injections into the other two were continued. These animals received six rat units each day without any increases. This same amount was also injected into one of the older males while injections were discontinued in the other two animals. After 36 days all but one male of each litter which had been continuously injected were sacrificed. These two males had by this time had 192 and 214 rat units of hormone respectively. These animals were carefully observed in the following days for signs of the descent of the testes into the scrotum.

#### OBSERVATIONS AND DISCUSSION

The injections caused no retardation of body growth of any of the animals as was reported by Bugbee and Simond (1926). All animals increased in weight, averaging about twenty-eight grams per two weeks for the older animals, and twenty-five grams for the younger rats. The males gained more weight than the females in both the injected and control animals. In the daily record there was an average increase of approximately two grams per day for all the animals.

When the animals were sacrificed it was invariably found that the thymus of the injected animal was smaller than that of the control (Figs. 1 and 2). The thymus of the control male of the larger litter weighed 0.231 grams as compared with 0.223 grams for that of the female control. The average weight of the thymus of the injected males was 0.182 grams as compared with

0.155 grams for the injected females. These were all under the same environmental conditions and killed within one day of each other. In the younger animals the thymus of the control male weighed 0.214 grams as compared with 0.203 grams for that of the female control. The average weight of the thymus of the injected animals was 0.170 grams for the females and 0.128 grams for the males. These weights are for those animals which were injected for twenty-four days. In the female which was injected for thirty-six days the thymus weighed 0.171 grams or approximately the same as the others. But in the male which was injected for 25 days after which injections were discontinued for eleven days, the thymus weighed 0.303 grams. This



FIGURES 1 AND 2

would tend to show that the injection of the hormone inhibits the growth of the thymus, but with the subsequent discontinuation of the injections, recovery seems to occur quite readily and quickly. This point should be checked in a greater number of animals.

The first manifestation of hormonal effects in the treated female animals was the opening of the vagina which occurred in the older animals after nine days of injections and in the

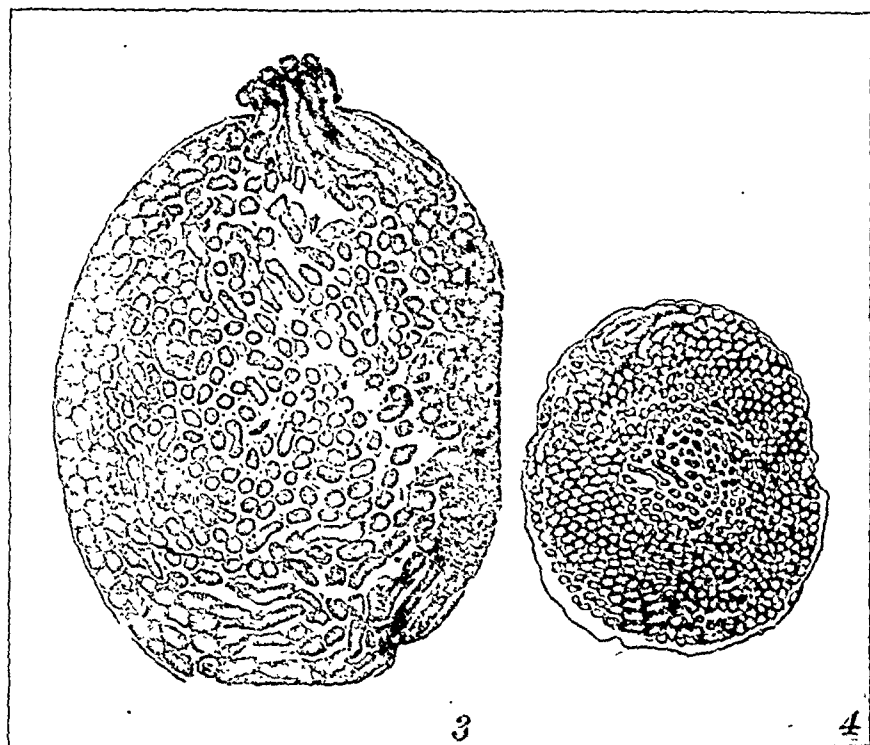
younger rats after 13 and 14 days. The vagina of the control animals at this period remained closed. Vaginal smears of the injected animals showed cornified cells which were sloughed off or desquamated from the lining mucosa of the vaginal wall. But after discontinuing the injections for observations on the after effects the daily smears showed a normal four-day oestrous rhythm for the following two weeks after which smears were discontinued.

Grossly there were no conspicuous changes observed in the ovaries of the treated animals except that they appeared to be smaller than the ovaries of the controls. But histologically the ovaries of all the animals were similar. They were characterized by a great number of developing follicles of various sizes and an abundance of interstitial tissue. The larger follicles appeared to be undergoing atresia. There were no corpora lutea in the ovaries of either of the injected or control animals, consequently ovulation had not occurred.

Histological preparations of the vagina and uterus showed a marked hyperplasia of these organs in the injected animals as previously described by Allen and Doisy, '24. It is evident from these results that the injection of ovarian and placental hormone into immature female rats induces growth of the vagina and uterus but in large doses over long intervals does not stimulate the growth of follicles in the ovaries.

In the males the size and weight of the genital organs of the control animals was twice and three times that of the injected rats (Figs. 3 and 4). The genital organs of the control animals of the older litter weighed 1.369 grams while those of the injected animals ranged from 0.401 to 0.672 grams. In the younger animals the genital organs of the control weighed 1.112 grams as compared with 0.203 and 0.163 grams for the injected animals. One male, which had been injected for 25 days, after which injections were stopped for eleven days, contained genital organs weighing 0.673 grams. The weights and sizes of the testes corresponded comparatively to that of the other genital organs. More noticeable than this condition, however, was that of the position of the testes in the various animals. In all animals which had had continued injections the testes remained in the abdomen, while the testes of the control animals descended into the scrotum. In the larger animals the weight of

the testes of the control averaged 0.974 grams, and measured 9x9x14.5 mm. and was in the scrotum when killed; while the weights of the testes of the injected animals ranged from 0.246 to 0.436 grams and measured from 4.5x5x8 to 6.5x7x10 mm. and were all located in the abdomen. In the animals in which injections were discontinued for eleven days the weight of the testes averaged 0.369 grams and measured 7x7x10 mm., but had just concluded the descent into the scrotum. With the younger



FIGURES 3 AND 4

animals approximately the same results were obtained and the time for the descent after discontinuing injections was about eleven days. Those animals in which injections were continued for 36 days and then discontinued, required 13 and 14 days for the complete descent of the testes into the scrotum.

That a block in the growth of the testes was produced was further shown histologically. There were no spermatozoa nor spermatids in the testes of injected animals (Fig. 4), while many spermatids and a few spermatozoa were found in the testes of

the control animals (Fig. 3). In the controls there were also numerous thick mitotic layers in the tubules and much interstitial tissue while in the injected animals there were very few mitotic figures and no interstitial tissue. In these animals where injections were discontinued for eleven days few spermatids were found in the tubules.

TABLE III

## Males

Rat	Treatment	Body Wts.		Wt. of Thy-mus Gm.	Wt. of Geni-tals Gm.	Wt. of Testes Gm.	Size of Testes MM.	Position of Testes
		At Start	At Death					
MN <sub>1</sub> R <sub>1</sub>	Control	21.5	99.8	.231	1.369	.971	9x9x11.5	In scrotum
MN <sub>2</sub> Na	Injected	20.0	83.7 After 4 weeks					11/23 stop injections 11/23 in abdomen 11/30 in abdomen 12/7 in scrotum
MN <sub>1</sub> La	Injected	21.0	82.1	.173	.672	.436	5x7x10	In abdomen
MN <sub>2</sub> R <sub>1</sub>	Injected	19.5	80.0	.192	.483	.261	5x6x8.5	In abdomen
MS <sub>2</sub> Ba	Injected	19.5	76.3	.183	.401	.216	5x5x8	In abdomen
M <sub>2</sub> Na*	Injected	20.0	112.5	.219	.836	.369	7x7x10	In scrotum
MN <sub>2</sub> Nb	Control	14.5	62.7	.212	1.112	.610	7x8x12	In scrotum
MS <sub>2</sub> REb	Control	15.0	61.6	.211	1.099	.436	5x7x12	In scrotum
MN <sub>2</sub> Rb	Injected	12.5	53.7	.122	.203	.061	3x3x5	In abdomen
MN <sub>1</sub> La	Injected	14.5	51.1	.131	.163	.064	3x3x6	In abdomen
MN <sub>1</sub> Lb	Injected	15.5	70.0 After 4 weeks					11/24 stop injections 11/24 in abdomen 12/7 in scrotum
M <sub>2</sub> Nb*	Injected	12.0	93.3	.303	.673	.295	5x7x10	In scrotum

\*All animals were killed after the last injection of extract, with the exception of animals M<sub>2</sub>Na and M<sub>2</sub>Nb, which were observed for 11 days before sacrificing. MN<sub>2</sub>Na and MN<sub>1</sub>Lb were not killed. These animals were also kept under observation after discontinuing injections.

## SUMMARY

This experiment consisted of injecting water-soluble preparations of hormone into male and female rats from two litters beginning at ages of 12 and 18 days. Injections were made twice a day starting with 2 rat units and increasing the dose daily for from 20 to 36 days. The total dose ranged from 74 to 214 rat units.

Some of the injected animals were killed for histological comparison with controls; others were observed for after effects.

In the males there was an inhibition of growth of the genital organs and the testes remained in the abdomen. This was obvious in the living and was further checked by weights, measurements and histological preparations. The genital organs

of the controls were much larger, and the testes descended into the scrotum during the experiment. Injected males observed after discontinuing injections required from 10 to 15 days for descent of the testes. After 20 days these testes appeared normal.

In injected females the vagina opened, while in the controls it remained closed. Vaginal smears during injections showed continuous oestrus; upon discontinuing injections, smears showed normal cycles. Histological sections of vagina and uterus showed same evidences of oestrous changes. There were no corpora lutea in the ovaries of either control or injected animals.

The weights of the thymus glands of injected rats were about half those of the controls.

The writers wish to acknowledge their indebtedness for the suggestions and assistance of Dr. Edgar Allen during the course of this work.

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# Abstract Department

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The comparative sensitiveness to epinephrin of blood pressure and intestinal motility in man. Dragstedt, C. A. and J. W. Huffman. *Am. J. Physiol.* 85: 363. 1928.

As previously reported, pressor effects in the unanesthetized dog may be obtained on sustained injection of epinephrin in the absence of intestinal inhibition. Danielopolu, Simici and Dimitri reported that in man 1 cc. of 1 to 300,000 adrenalin exaggerated the peristaltic contractions of the small intestine, but that 1 cc. of 1 to 100,000 produced an inhibition. They did not report simultaneous observations on blood pressure. Csepai reported that with intravenous injections in man, the average patient gave a rise in pressure of 20 to 30 cm. of water with 1 cc. of 1 to 100,000 epinephrin. No simultaneous observations of intestinal motility were reported. We have made simultaneous observations of blood pressure and intestinal motility in man after injection of epinephrin, and have seen blood pressure rises of 15 mm. in the absence of any effect on intestinal motility.—Authors' Abst.

Vasomotor responses to perfused adrenalin in the unanesthetized dog. Durant, R. R. and J. H. McNinch. *Am. J. Physiol.* 85: 364. 1928.

The spleens of two young female dogs were externalized by the method described by Barcroft and Stephens. After a short recovery period, during which the incisions had healed completely, the volume changes of the spleens were recorded by means of an oncometer strapped to the abdominal wall. Blood pressure was recorded separately and also simultaneously with the spleen volume, by the direct method. The cannula was inserted in the femoral artery under local novocain anesthesia. Intravenous injections of minimal doses of adrenalin (Parke, Davis & Co.) were found to produce only rises in blood pressure and constriction of the spleen. These observations confirm those of Dragstedt and lend support to the "emergency" theory of suprarenal function.—Authors' Abst.

The accumulation of sulphur in the skin after adrenalectomy (*L'accumulation du soufre dans la peau apres surrenalectomie*). Loeper, M., J. Decourt and A. Lesure. *Compt. rend. Soc. de biol.* 98: 1098-1099. 1928.

In three dogs there was a marked increase of sulphur in the skin following the removal of one adrenal.—J. C. D.

**Muscular fatigue in decapsulated rabbits** (*La fatigue musculaire chez les Lapins privés de capsules surrénales*). de Mira, F. and J. Fontes. *Compt. rend. Soc. de biol.* 98; 987-989. 1928.

**Action of adrenin on the activity of fatigued muscle in decapsulated rabbits** (*Action de l'adrénaline sur la contractilité du muscle fatigué chez le Lapin privé de capsules surrénales*). de Mira, F. and J. Fontes, *Compt. rend. Soc. de biol.* 98: 1011-1013. 1928.

**Further observations on the relation between the adrenals and muscular action** (*Nouvelles recherches sur les capsules surrénales dans leurs rapports avec la fonction musculaire*). de Mira, F. and J. Fontes. *Compt. rend. Soc. de biol.* 98; 1013-1015. 1928.

Flexor muscles of the foot were used in anaesthetized animals and their activity under electrical stimulation recorded on an ergograph. Compared with controls, the decapsulated animals showed three types of reaction according to whether the adrenal insufficiency was slight, marked, or very severe. (a) The muscle became rapidly exhausted, but recovered its initial power after a short rest. (b) The rapid exhaustion of the muscle as in (a) was followed by failure to recover after rest. (c) The initial reaction was very weak and there was no recovery after rest. Injections of adrenin extract, of whole gland and extract of cortex, failed to relieve the fatigue, and in most cases actually hastened it.—J. C. D.

**Studies on adrenal insufficiency. VI. The influence of "heat" on the survival period of dogs after adrenalectomy.** Rogoff, J. M. and G. N. Stewart, *Am. J. Physiol.* 86: 20-24. 1928.

"Heat" in four dogs was associated with a marked lengthening of the survival period and the period of good health after removal of the adrenals. One lived into the 22nd day after excision of the second adrenal; one lived 32 days; one lived into the 37th day, and one into the 65th day. Nothing like these survival periods was seen in about 150 control dogs.—R. G. H.

**Studies on adrenal insufficiency. VII. Further blood studies (cholesterol and calcium) in control adrenalectomized dogs.** Rogoff, J. M. and G. N. Stewart, *Am. J. Physiol.* 86: 25-31. 1928.

The calcium content of the blood serum of 12 adrenalectomized dogs was generally found increased at the time of or sometimes a little preceding the development of the serious symptoms, especially anorexia, which terminate the period of good health. No significant change in blood cholesterol was found.—R. G. H.

**The effect of adrenaline on an isolated heart after thyroidectomy** (*Die Reaktion des isolierten Herzens eines thyreoidektomierten*



Tieres auf Adrenalin). Schermann, S. J., Arch. f. exp. Path. u. Pharmakol. 126: 10. 1927. Abst., Physiol. Absts. 13: 181.

The threshold dose of adrenaline in the isolated heart of the rabbit was determined. In the case of 6 rabbits whose thyroids had been removed 15 to 70 days before, it was 20 to 50 times higher than in the case of 6 rabbits who had undergone a similar operative technique without actually losing their thyroids.

The effect of thyroidectomy and of forcing fluid on the susceptibility to toxins in suprarenalectomized rats. Wyman, L. C., Am. J. Physiol. 85: 413-414. 1928.

It has recently been shown (Corey, Zwemer, 1927,) that forcing fluids or thyroidectomy (thereby decreasing elimination of water) prolongs the life of suprarenalectomized cats. Dehydration is one of the symptoms of suprarenal insufficiency in rats. In a series of 30 rats which had been completely thyroidectomized one or two weeks previous to double suprarenalectomy, 40 per cent died of acute or subacute suprarenal insufficiency within 21 days after the latter operation. These animals showed the usual symptoms of acute or subacute insufficiency and at death the usual number showed such findings as diarrhea, bloody nose and eyes, and congested stomach and intestines. Of those which survived, 10 had gained weight in the period between thyroidectomy and suprarenalectomy, but during the three weeks following suprarenalectomy 10 lost weight and only 3 gained. Of these latter one was found at autopsy to have gross accessory cortical tissue. In a series of 137 control rats which had been doubly suprarenalectomized without previous treatment, 42.3 per cent died of acute or subacute suprarenal insufficiency. The lethal dose of diphtheria toxin, administered intraperitoneally, averaged 2.75 M.L.D. per gram of body weight both for the thyroidectomized-suprarenalectomized rats and for the suprarenalectomized rats. The lethal dose for normal or blank operated rats averaged 6 M.L.D. per gram of body weight. Both sets of suprarenalectomized rats were, therefore, 2.18 times as susceptible to diphtheria toxin as the controls. Both thyroidectomized-suprarenalectomized rats and suprarenalectomized rats were killed quite regularly by doses of 7 mgm. of histamine acid phosphate per hundred grams of body weight. All which survived such doses were shown at autopsy to have gross accessory suprarenal tissue. Normal or blank operated rats survived doses of histamine acid phosphate up to 100 mgm. per hundred grams of body weight. Fluid was administered to rats by means of daily intraperitoneal injections of 10 cc. of a 5 per cent solution of glucose during a period of three to five days at two to four weeks after double suprarenalectomy. Following this treatment, the rats were killed by doses of from 5 to 10 mgm. of histamine acid phosphate per hundred grams of body weight. Preliminary experiments indi-

cate that similar administration of glucose solution does not decrease the heightened susceptibility of suprarenalectomized rats to diphtheria toxin. It appears that thyroidectomy does not decrease the acute and subacute mortality percentage after suprarenalectomy. Also, thyroidectomy or forcing fluids does not decrease the heightened susceptibility of suprarenalectomized rats to the toxins investigated. This suggests that impaired ability to flush toxins out of the body, due to dehydration, is not an important part of the picture of increased susceptibility.—Author's Abst.

The effect of suprarenal insufficiency on the oestrous cycle in the albino rat. Wyman, L. C., *Am. J. Physiol.* 85: 414-415. 1928.

Of a series of 14 doubly suprarenalectomized female rats which were exposed to males two weeks after operation, 7 became pregnant and gave birth to normal litters. Of the 7 that did not become pregnant, 4 died of subacute suprarenal insufficiency within two weeks after exposure to the males. The other 3 were left with the males for two or three months and were then killed. At autopsy no gross accessory suprarenal tissue was found. In 6 of the group that had litters gross accessory cortical tissue was found at autopsy. These results suggest that ability to reproduce after double suprarenalectomy is correlated with the degree of suprarenal insufficiency remaining after operation. In a series of 17 female rats, daily vaginal smears were studied, both before and after double suprarenalectomy. Fourteen of this group died of acute or subacute suprarenal insufficiency within 27 days after operation. With one exception these rats showed no oestrous changes in the vaginal smears from the time of operation until death. In the one case the smears were characteristic of oestrous for the 7 days preceding death. In the 3 rats that survived longer, there were dioestrous pauses after operation lasting from 21 to 36 days, following which oestrous changes appeared at irregular intervals and were separated by much prolonged dioestrous pauses. These rats were exposed to males and 2 became pregnant. One of these gave birth to a normal litter and at autopsy was found to have a large accessory suprarenal mass; the other died of chronic suprarenal insufficiency on the seventeenth day of pregnancy. In order to control for operative trauma, the vaginal smears were studied as before in a series of 12 rats in which one suprarenal gland was removed and the other gland was exposed and handled. This procedure did not disturb the regular occurrence of vaginal oestrous changes. The remaining suprarenal gland was later removed. Following this, 5 rats died of acute or subacute suprarenal insufficiency. In 2 of these there was no change in the occurrence of oestrous changes other than a slight prolongation of the oestrous period. The other 3 had prolonged dioestrous pauses. Of the 7 that survived, 3 showed no significant changes in the occurrence of vaginal oestrous changes and 4 had occasional

much prolonged dioestrous pauses. It appears that in suprarenal insufficiency in the albino rat there may be partial or total inhibition of vaginal oestrous changes, presumably due to suppression of ovulation. It is not known whether there is a direct relationship between the functioning of the suprarenal gland and the production of ovarian hormones or an indirect relationship through the mediation of other factors. The irregularity of the effect of suprarenalectomy suggests the latter.—Author's Abst.

Endocrine and biochemical studies in schizophrenia. Bowman, K. M., *J. Ner. & Ment. Dis.* 65: 465-483; 585-604. 1927.

A study of twenty-four cases of schizophrenia was made, using tests which would have a special relationship to endocrine function. An abnormally low level of basal metabolism was found in half of the cases, with a tendency towards low or minus readings in nearly all the other cases. Nearly one-half of the cases showed an abnormal blood sugar curve, all but one being of the "sustained" type. Over one-third showed a positive galactose tolerance test. X-ray examinations and gastric analyses showed a definite functional disorder of the gastro-intestinal tract in about half of the cases and questionable functional disorders in all but two of the other cases. X-ray examinations further revealed infected teeth in 40 per cent of the cases, with questionable infection in 10 per cent more. X-ray examinations also revealed "dropped" hearts in 30 per cent of the cases, questionable pulmonary tuberculosis in 13 per cent and healed pulmonary tuberculosis in 4 per cent (one case). The findings are not consistent with the constant presence of any definite endocrine disorder, and do not suggest that a simple glandular dysfunction of a constant type is an etiological factor in schizophrenia. Rather they suggest that many functional disorders, closely linked up with the endocrine system, are frequently found and that schizophrenia is not a specific endocrine disease, but may arise on a number of different bases. The one constant finding appears to be that a metabolic disorder of varying degree is nearly always present as manifested in functional gastro-intestinal disorders and a tendency toward low basal metabolism which are present in the majority of cases.—Author's Abst.

Histological changes in the female reproductive organs under the influence of the hormone of the corpus luteum (*Modifications histologiques du tractus genital femelle sous l'action de l'hormone du corpus jaune*). Gley, P., *Compt. rend. Soc. de biol.* 98: 834-837. 1928.

In the female rat, daily injections of corpus luteum extract inhibit the growth of Graafian follicles so that only undeveloped or small sized ones are found. The uterus and the vagina resembles those of a spayed animal. Evidently the normal oestrous cycle is

dependent on the follicular hormone, which brings about oestrous, and the hormone of the corpus luteum, which causes regressive changes. This regression goes on until the corpus luteum degenerates and the follicular hormone again begins to act.—J. C. D.

**Cytological studies on the human corpus luteum** (*Recherches cytologiques sur le corps jaune de la Femme*). The ovarian and uterine cycles in the human (*Cycle ovarien et cycle utérin chez la Femme*). Horrenberger, R., *Compt. rend. Soc. de biol.* 98: 849-851. 1928.

The cells of the corpus luteum show an active phase characterized by "chondriocontes" and mitochondria and a phase of involution in which these disappear and fatty degeneration takes place. In the thecal cells similar changes occur, but they precede those in the lutein cells. The uterine cycle ends with menstruation and that of the ovary with the degeneration of the corpus luteum. These cycles are occurring simultaneously and the ovarian cycle is influencing the uterine. Ovulation occurs at a variable time in the intermenstrual period and is to a certain extent independent of the formation of the corpus luteum.—J. C. D.

**Effect of lutein injections on oestrous cycle of the guinea pig.** Macht, D. I., A. Stickel and D. Seckinger. *Am. J. Physiol.* 85: 389-390. 1928.

The oestrous cycle in guinea pigs was studied over a period of several years by the vaginal smear method of Papanicolaou, Stockard and others. Water-soluble extracts of corpus luteum were obtained by two methods. According to one method, freshly desiccated corpus luteum was extracted with petroleum ether, then with pure ether and again with pure ethyl acetate, evaporated to dryness, the residue taken up in aqueous bicarbonate solution and finally neutralized with hydrochloric acid. In the second method, the corpus luteum was extracted with weak alcohol deproteinized with subacetate of lead, freed from excess of lead with sulfuric acid, evaporated on the water bath to remove alcohol, and again neutralized. Corpus luteum was obtained in the fresh state from cows in some experiments and from the pig in others. Control experiments were made with injections of follicin and extracts of ovarian residue, placenta and various glands. Daily injections intraperitoneally of 1 cc. of the aqueous lutein solution (equivalent to 5 mgm. of the residue) produced a distinct inhibition of the oestrous cycle, which was suppressed in some animals for as long as seventy or more days. When the injections were discontinued, the normal cycle was quickly re-established. In the present investigation only perfectly healthy animals were used, as it was found that when the animals were diseased the oestrous cycle became very irregular.

—Authors' Abst.

Experiments with follicular and placental extracts. Oslund, R. M.,  
Am. J. Physiol. 85: 398. 1928.

Feeding of follicular or placental extracts is ineffective. Young female rats were given five unit doses of Estrogen (Parke, Davis & Co.) per day over a period of five days. No oestral changes were found by the vaginal smear method. Estrogen applied to the vagina in minimal doses was followed by positive oestral changes. Though follicular and placental extracts when injected subcutaneously or intraperitoneally, or when applied to the vagina, invoke positive oestral changes, as determined by the vaginal smear method, they do not bring about receptiveness on the part of the female for the male. In three series of spayed rats (18 rats) and in four series of unoperated rats (30 rats), all of which gave positive oestral smears over a period of from one to ten days, all females vigorously fought off males four or five times daily. In another series, five rats were spayed and autotransplants made of their ovaries. One month later they were kept in oestrus over a period of nine days. One rat of this series received several males on the seventh day. All others vigorously fought off males four or five times daily. That the failure to obtain positive copulatory results did not lie in the extract was determined by injecting fresh follicular fluid obtained from hog ovaries. The same results were obtained.

—Author's Abst.

Importance of the site of attachments of testicular transplants (L'importanza della sede per l'attecchimento dei trapianti testicolari).

Trichera, C., Policlinico (sez. chir.), 33: 484-496. 1926. Abst., Biol. Absts. 1: 1066.

Transplants in the dog were made by the technique of Voronoff not only on the vaginal serosa, but on the parietal peritoneum, parietal pleura, subcutaneous, intramuscular, perirenal fat, bone marrow, and in the parenchyma of spleen and of testicle. After an equal lapse of time (1 month) histological examination of the transplants have uniformly shown a pure involution of the epithelial cells with their more or less rapid resorption until complete disappearance; and a corresponding proliferation of the connective tissue of the host organ, which finally penetrated the intertubular spaces. An increased libido resulted, whatever the site of the transplant. If the hormone function of the testicle belongs to its epithelial elements, as urged by some, these results are thought definitely to contradict Voronoff, who postulates a specificity of site of transplant; for, it is found, that transplants from all sites, including the vaginal, gave homologous results.

What should one think of the "heart hormones"? (Que doit-on penser des "hormones cardiaques"?). Mouzon, J., Presse med. 37: 582. 1928.

Mouzon reviews the literature and gives an extensive bibliography on the subject. He concludes that it would be premature, at present, to draw conclusions concerning the usage of myocardial extracts in cardiological therapeutics, or even concerning any of the products precociously misnamed "heart hormones." However, in spite of the controversies which continue to render the question difficult, the experimental facts now permit a careful study of the hormone factors which act on the mechanism of heart contractions. One may follow with interest the work, which will, some day, give a true physiological medication of the myocardium.—R. G. H.

**Quantitative estimation of posterior pituitary lobe secretion in cerebrospinal fluid of epileptics (Der Gehalt des Epileptikerliquors an Hypophysenhinterlappensekret).** Altenberger, H. and F. Stern. *Ztschr. f. d. ges. Neurol. u. Psychiat.*, 112: 691-710. 1928.

The cerebrospinal fluid of 80 non-epileptics examined by the oxytocic method showed pituitrin-like substance in 71 instances, with an average strength in lumbar fluid of 580  $\mu$ mgm. (micromilligrams) (64 specimens: 10-1,000  $\mu$ mgm.), and in ventricular fluid 870  $\mu$ mgm. (7 specimens: 50-1,000  $\mu$ mgm.). In 39 of 80 epileptics the substance was found to average 520  $\mu$ mgm. (160-1,400  $\mu$ mgm.) in lumbar fluid, while in 40 lumbar, suboccipital, or ventricular fluid was found inactive. The authors believe that pituitary hypofunction must be added to the list of exciting factors for epileptic seizures.

—A. J. McLean.

**Further observations on the diuretic substance of experimental diabetes insipidus.** Bourquin, H., *Am. J. Physiol.* 85: 354-355. 1928.

The following additional properties of the diuretic substance present in the blood and in extracts of the mammillary bodies and adjacent tissue of the brains of dogs suffering from experimental diabetes insipidus have been demonstrated. It is precipitated from solutions made weakly alkaline with barium hydroxide; is insoluble in ether, acetone, and ethyl alcohol; is completely destroyed by ashing; and is labile in solutions strongly alkaline even at room temperature, and in neutral extracts of the mammillary bodies allowed to stand at room temperature. The freshly secreted urine of dogs suffering from experimental diabetes insipidus, evaporated to a small volume, treated with ten or more volumes of cold ethyl alcohol to remove the toxic substances, redissolved and filtered to remove the proteins, causes a prolonged diuresis accompanied by pronounced thirst when injected intravenously into normal dogs. Control injections of urine secreted over the same period of hours by a normal dog of the same weight, in which diuresis has been induced by giving water per orum, causes a comparatively slight and very transitory diuresis unaccompanied by thirst. This substance

is presumably identical with the diuretic substance present in extracts of the mammillary bodies and in the blood of these dogs, for it possesses the same properties. A diuretic substance also having these same properties has been demonstrated in extracts from the mammillary bodies and adjacent tissue taken from the brains of freshly slaughtered hogs, sheep, and cattle, but not in extracts of similar quantities of tissue selected at random from other portions of the same brains. The substance is present in comparatively small amount, for the extract from five to six hundred hog brains produces about the same degree of diuresis as that which is caused by the extract from the mammillary bodies of the brains of three to five diabetic dogs.—Author's Abst.

The effect of daily transplantation of the anterior lobe on the course of pregnancy in the rat and mouse. Engle, E. T. and Camille Mermod. *Am. J. Physiol.* 85: 518-526. 1928.

Daily homeotransplants of fresh anterior lobe of pituitary were given to 45 mice and 25 rats. If given in the first third of pregnancy, implantation or early resorption of the ova occurred. If treatment is begun during the middle third of the period of gestation, resorption or expulsion of the fetus took place. Pregnancy was interrupted less often when treatment was begun in the latter third of pregnancy. Many normal litters were born at term in this series. It is thought that abortion or resorption would occur in every case were a sufficiently large amount of hormone introduced. The gonad-stimulating hormone of the anterior pituitary, introduced by the fresh transplant method, resulted in the production of a large number of ovarian follicles. The ovarian hormone thus produced caused a proliferation of the uterine mucosa, bringing about a condition similar to that in normal oestrus. Pregnancy appears to be incompatible with these conditions. Many tubal ova were found in those cases which were studied microscopically after abortion had occurred. Ovulation did not occur during pregnancy, but followed its termination.—R. G. H.

Contribution to the study of the function of the anterior lobe of the hypophysis (*Contribution à l'étude du fonctionnement du lobe antérieur de l'hypophyse*). Grueter, F., *Compt. rend. Soc. de biol.* 98: 1215-1217. 1928.

Aqueous extracts of the anterior lobe were injected into immature female rabbits. In the former, there was a remarkable development in the number of ripening follicles and corpora lutea accompanied by marked congestion of the genital tract. In the latter, injection resulted in suspension of oestrous, development of corpora lutea in large numbers, and appearance of milk in the mammary glands.—J. C. D.

**Physiology and pathology of the pituitary** (*Beitrage zur Physiologie und Pathologie der Hypophyse*). Poos, F., *Klin. Wchnschr.* 6: 1884. 1927. Abst., *Physiol. Absts.* 13: 183.

A summary is given of a long series of observations on the histological changes in the pituitary which result from interference with the function of other ductless glands. The experiments were done on cats, dogs, rabbits and rats. The effects of thyroidectomy, parathyroidectomy, castration, pregnancy, pancreatectomy, paraneephrectomy, certain combinations of these, and brain incisions, were investigated. The principal findings were as follows: The pituitary always reacts qualitatively in the same way to various endocrine disturbances. Quantitative variations in the reaction of the pituitary depend on the severity of the lesion in other endocrine glands, the duration of the lesion, and the age and species of animal used. All parts of the gland react together. The first phase is an increased functional activity (increase of eosinophils and secretory stage of gland cells). Increase in size being limited by its surroundings, the first phase is followed by structural alterations due to pressure; these are, in order of occurrence, oedema, degeneration, and pigment formation. The reaction to parathyroidectomy is stronger than to thyroidectomy. The secretion of the middle lobe only appears as colloid when increased production and interference with absorption occur. This secretion is removed via the blood stream. The changes undergone by the gland in pregnancy are essentially the same as those produced by other endocrine disturbances, and are not specific. The cysts in the pituitary which are commonly met with in cats and dogs may grow markedly as a result of disturbances in the endocrine system as well as during pregnancy.

**Further report of a case of experimental canine gigantism.** Putnam, T. J. and E. B. Benedict. *Am. J. Physiol.* 85: 401. 1928.

A sterile extract of the anterior lobe of beef hypophysis has been administered intraperitoneally to a thoroughbred bulldog, in doses up to 55 cc. daily, for about a year. The treated animal has outgrown her litter-mate sister control by 60 to 90 per cent, and shows changes in the bones, skin, nipples and vagina which might be interpreted as acromegaloid. Some of the disabilities of experimental hypopituitarism in dogs can be mitigated by injections of a similar extract.—Authors' Abst.

**Presence of melanophore-expanding and uterus-stimulating substance in the pituitary body of early pig embryos.** Snyder, F. F., *Am. J. Anat.* 41: 399. 1928.

Melanophore-expanding and uterus-stimulating substances are found in the pituitary of pig embryos of 30 mm. crown-rump length; i. e., when the foetus is about one-tenth its length at birth and when the weight of a single gland is roughly 0.05 mgm. This was



determined by perfusing "albino" (hypophysectomized) tadpoles and normal adult frogs and by employing the guinea-pig uterus test for oxytocic action.—W. J. A.

**Loosely-bound sulfur in pituitary extracts.** Sullivan, M. X. and M. I. Smith. Pub. Health Rep. 43: 1334-1342. 1928.

Tests were made on 0.25 per cent acetic acid extracts of some thirty-three samples of pituitary powders made according to the U. S. P. X. method of preparing extracts from standard pituitary. The preparations comprised (1) five samples of standard powdered pituitary; (2) a fresh gland extract, 1 cc. of which represented the physiological activity of 7 mgm. of standard powdered pituitary; (3) a sample of a commercial powder which when assayed was found to be of standard potency; (4) two commercial samples physiologically inert; (5) a commercial sample having a slight and almost negligible oxytocic activity; (6) eleven commercial samples of posterior pituitary with different degrees of physiological activity; (7) twelve commercial samples of desiccated anterior pituitary. These extracts were tested, qualitatively, chemically, and physiologically. The physiological criterion mainly relied on was the power to raise the blood pressure when injected intravenously into an anesthetized dog. The chemical test for loosely-bound sulfur was as follows: To 2 cc. of the extract in a small test tube there were added 0.1 cc. of half saturated lead acetate and 1 cc. of sodium hydroxide (usually normal), and the tube was placed in boiling water. Potent extracts begin to brown in 16 seconds and give a black precipitate of lead sulfide within three minutes. Inactive preparations do not show such a coloration. Extracts of commercial posterior lobe, when active, give a positive lead sulfide test, but not as strong, as a rule, as the standard powders. The commercial powders, as a rule, were less active physiologically. Extracts of the anterior lobe, as a rule, give no lead sulfide. In a few cases they gave a slight positive test. Whether the relationship indicated between the physiological test and the chemical test, is coincidental or is an indication that the physiological activity of the posterior pituitary is tied up with the presence of highly reactive sulfur compounds remains for further investigation. In either case, the test for highly reactive sulfur should be useful in the isolation and purification of the active principles.—Authors' Abst.

**Massive dosage with insulin.** Byworth, H. A., Brit. M. J. 1: 801. 1928.

The author reports a case of diabetes in a man 23 years of age who entered the hospital in a semi-comatose condition. In the course of 36 hours he was given 1,715 units of insulin. Pulmonary tuberculosis and a multitude of small ulcers on his arms and legs

(due likely to insulin injections, the author thinks) were present, which may explain his tolerance to such a huge dosage of insulin.  
—H. J. J.

**Oral administration of pancreatic and other preparations in treatment of diabetes.** Fuller, C. B. S., Brit. M. J. 1: 798. 1928.

The author worked with several oral pancreatic preparations in an attempt to determine their influence on blood sugar level and the general improvement of tolerance in the patient. Hourly blood sugar estimations were made with the varied preparations, but all with negative results. The first paragraph of his conclusions summarizes best his findings: "From the consideration of the data given it is clear that the administration of oral preparations of pancreas in severe cases of diabetes is a waste of time, and likely to be harmful to the patient by delaying the proper treatment with diet and insulin injections."—H. J. J.

**Changes in glycemia seen in depancreatized dogs which carry pancreatic grafts following operation and ingestion of glucose** (*Variations de la glycémie chez les chiens dépancréatés porteurs d'une greffe pancréatique, apres l'opération et a la suite d'ingestion de glucose*). Kepinov, L. and S. P. Dutailis. Compt. rend. Soc. de biol. 98: 1193-1195. 1928.

In depancreatized dogs with pancreatic grafts, ingestion of glucose results in a sharp rise in blood sugar followed by a hypoglycemia. This, in turn, is followed by a considerable increase in blood sugar, which does not disappear for several days. The latter rise is not seen in normal animals.—J. C. D.

**Answer to Gayet and Guillaumie on the regulation of the internal secretion of the pancreas** (*Réponse a la note de R. Gayet et M. Guillaumie sur la régulation de la sécrétion interne pancréatique*). LaBarre, J., Compt. rend. Soc. de biol. 98: 859-861. 1928.

The author quotes his previous work to show that, contrary to the above writers, the normal secretion of the islet tissue is under control of the central nervous system, since it ceases as soon as the vagi are cut.—J. C. D.

**Hypertrophy (adenoma?) of the islands of Langerhans with associated hypoglycemia.** Norris, G. W. and W. U. McClenahan, Proc. Assoc. Am. Physicians, May, 1928. Abst., J. A. M. A. 91: 50. 1928.

A colored man, aged 41, gave a history of periodic attacks of loss of memory of a gradual onset, which generally lasted one and a half hours, occurred usually at midday and were relieved by taking food. Between attacks he was free of symptoms. The physical examination was essentially negative on admission. The following

day the patient fell into coma from which he never recovered. The blood sugar showed 40 mgm. of sugar per 100 cc. on this day. He developed terminal broncho-pneumonia and died seventy-two hours after admission. The spinal fluid examination was negative, except for a low sugar content (20 mgm. per 100 cc. of fluid). In spite of the administration of dextrose by gavage, enteroclysis and intravenously, the hypoglycemia persisted and sugar determinations were 40, 46 and 38 mgm. per 100 cc. on the three successive days. At autopsy a partially encapsulated, vascular nodule, measuring 17 by 5 by 10 mm., was found in the pancreas, composed of cells similar in structure and arrangement to those of the islands of Langerhans, and associated with a generalized hyperplasia of the islands throughout the pancreas. The suprarenals and pituitary were negative. There was no evidence of metastasis, and the eosin and hematoxylin stains of the liver failed to show a significant decrease in its glycogen content. The analysis of both the pancreas and the tumor tissue for their insulin content was attempted, but was unsuccessful. The finding of a lesion of the pancreatic islands in this case, associated with hypoglycemia and a very significant history, would seem to add further evidence toward the recognition of a new disease entity.

**Carcinoma of the islands of the pancreas.** Thalhimer, W. and F. D. Murphy. *J. A. M. A.* 91: 89-91. 1928.

After two and a half years of gradually increasing severity of symptoms, a patient developed a state of almost constant semistupor, accompanied by frequent convulsions and marked hypoglycemia, until death followed, apparently from exhaustion. At necropsy, the only significant pathologic lesion found was a small primary tumor of the pancreas. Its microscopic appearance indicated that it originated from the cells of the islands of Langerhans, and that the tumor is either a carcinoma or a low grade of malignancy, or else an adenoma. It is believed that the active secretion of insulin by these tumor cells caused a hyperinsulinism which resulted in hypoglycemia and, finally, in death.—Authors' Abst.

**The direct stimulation of the islands of Langerhans by adrenin** (*Action stimulante directe de l'adrénaline sur les îlots de Langerhans*). Zunz, E. and J. LaBarre. *Compt. rend. Soc. de biol.* 98: 858-859. 1928.

The donor (dog) was decapsulated and the recipient depancreatized. Then the pancreatic circulation of the donor was connected with the carotid-jugular circulation of the recipient. Injection of adrenin chlorhydrate in the recipient resulted in a hypoglycemia.—J. C. D.

The effect of ligation of the common bile duct upon the appearance of tetany in thyroparathyroidectomized dogs. Brougher, J. C., *Am. J. Physiol.* 86: 39-41. 1928.

Ligation of the common bile duct with or without cholecystectomy prevented the appearance of parathyroid tetany in 5 dogs. In 3 mild tetany occurred. This delay in the appearance of tetany may be attributed to one or all of the following factors: (a) a lessened excretion of calcium from the body by way of the bile; (b) increased absorption of calcium from the gut because of the absence of the alkaline bile acids, which precipitate calcium; (c) depression of the nervous system by the absorbed bile.—R. G. H.

The effects of selective solar irradiation on the parathyroid glands of chicks. Higgins, G. M. and C. Sheard, *Am. J. Physiol.* 85: 299-310. 1928.

Studies are reported on the influence of selective solar irradiation on the parathyroid glands of chicks. The chicks were kept within doors behind amber, blue, ordinary glass and vitaglass, which transmit known portions of the sun's spectrum. The basic diet used throughout the experiment was the Wisconsin all-mash ration. Half of the chicks under each filter were fed the basic diet alone, while the other half were fed the basic diet and 2 per cent by weight of cod-liver oil. All the chicks of each pen thrived equally well during the earlier months of the experiment; signs of weakness of the legs did not develop until they were five months old. Enlargement of the parathyroid glands was recognized within the first few weeks in chicks growing under amber and blue glass; this enlargement was due to hyperplasia rather than hypertrophy. The 2 per cent of cod-liver oil added to the basic diet serves to maintain a more nearly normal sized gland even in the longer wave lengths of sunlight. Both the longer and the shorter wave lengths of sunlight are essential to the maintenance of normal parathyroid glands. Regression of the cell columns is manifested early; the cause is undetermined. Cysts accompany the retrogressive processes that ensue within the gland. These cysts are of two types. One is walled off from the remaining portion of the gland by definite columnar epithelium, while the other is enclosed by a series of concentrically arranged flattened cells. There was no organic indication either in blood calcium, blood phosphorus or general activity that such parathyroid hyperplasia had arisen.—Authors' Abst.

Tissue changes in parathyroid tetany and in guanidine poisoning. Larson, E. and L. A. El Gourie. *Am. J. Physiol.* 85: 387-388. 1928.

A series of dogs, cats and rabbits was injected subcutaneously with fatal doses of guanidine hydrochloride. Three dogs were thyroparathyroidectomized and allowed to die in an acute attack of tetany. Both of these series of animals were autopsied immediately

and tissues saved for microscopic examination. Any gross changes were noted. The tissues of the animals dying of guanidine poisoning showed the following changes: The kidneys presented a condition of simple necrosis of the tubules, with the glomeruli little affected and no congestion. The liver, in every case, exhibited fatty degeneration at the periphery of the lobules and simple necrosis at the center. The spleens showed no striking changes. The adrenals were in varying stages of simple necrosis. The testes and epididymides appeared normal. Examination of these tissues from the dogs dying of parathyroid tetany revealed the following changes. Both the glomeruli and the tubules of the kidneys were greatly congested, with necrosis of the cells of the tubules. The livers were congested to a great degree. Simple necrosis of the hepatic cells were, apparently little affected. The spleens, in every instance, were immensely congested with the presence of blood pigment. The adrenals were likewise congested. The various areas presented varying degrees of necrosis. There were marked differences between the microscopic findings in the viscera of animals dying of parathyroid tetany and those dying of guanidine poisoning.—Authors' Abst.

**Interrelations of calcium, phosphorus and sugar in parathyroidectomized dogs.** Reed, C. I., *Am. J. Physiol.* 85: 402. 1928.

In an effort to explain the nature of the adaptation occurring in latent tetany when animals survive without restoration of normal proportions of calcium and phosphorus, it was noted that ingestion of 2 gm. per kgm. of glucose frequently relieved dogs from an attack of tetany within 30 minutes to 2 hours. In controlled dextrose tolerance tests it was found that during an attack of tetany there was decreased tolerance, which was usually at the peak at the end of 2 hours, while in normal dogs and those not in tetany this point was found to occur at about the end of the first hour. The fasting blood sugar level was not affected by parathyroidectomy. All fractions of phosphorus were decreased in concentration from 10 per cent to 50 per cent. Calcium was not greatly affected in normal dogs, but after operation there was a tendency to fluctuations, with ultimate diminution. The action was usually completed in two hours. The diminution in concentration of inorganic phosphorus was usually sufficient to raise the Ca:P ratio to a higher figure and relief from tetany may, at present, be assigned to this factor. In order to determine the effect of a decreased blood sugar concentration, insulin was injected subcutaneously. In both normal and operated dogs, with and without tetany, dextrose and inorganic phosphorus concentrations were lowered. In tetany the calcium concentration tended to fluctuate, while in normal and operated dogs not in tetany this factor was invariably increased. In every case of tetany the net result of insulin injection was an increase of the Ca:P ratio, which, if great enough, resulted in relief from tetany.

—Author's Abst.

The thyroid and pregnancy (*La thyroid au cours de la grossesse*).

Bernard, W., *Rev. franç. d'endocrinol.* 5: 395. 1927.

The author records his personal observations in two parts: (1) Histological changes in the thyroid of the dog during pregnancy, and (2) the effect of partial thyroidectomy on pregnancy in guinea pigs. He shows there is cyclic change in the glandular structure; in dioestrus the follicular cells are large and the follicle is well filled with colloid; three days after coitus there is in many cases a change in the number and volume of vesicles; at thirty-two days the follicular cells are much changed, the follicle itself becoming much enlarged; at forty-three days the cells and follicles have regained much of their dioestrus appearance, while the interstitial cells have multiplied rapidly; a few days after delivery the thyroid returns to the normal dioestrus appearance. The author reports that partial thyro-parathyroidectomy in guinea pigs prolongs the gestation period as much as eight days.—B. Cunningham.

Thyroid disease. An experimental study. Cooksey, W. B. and M. S. Rosenblatt. *Arch. Int. Med.* 42: 1-13. 1928.

The question of excessive thyroid secretion in exophthalmic goiter and allied diseases is discussed, and the various claims for and against hyperthyroidism are presented. Feeding experiments were conducted in which various types of goitrous glands from human beings were fed to tadpole larvae. There is evidence from these experiments that thyroid glands from clinically active cases of goiter contain more active thyroid principle per unit weight than the normal thyroid. Other goitrous glands contained less active principle by this biologic test, and the amounts were directly proportional to the clinical activity of the patient. Old non-toxic adenomas contained less active principle per unit weight than normal, while one gland which had had much roentgen-ray treatment and rest also contained less active principle per unit of weight. By these experiments, hypersecretion of the thyroid gland in exophthalmic goiter and other clinical thyrotoxic cases seems definitely proved.—Authors' Summary.

The influence of thyroidectomy on tissue respiration. Dye, J. A. and R. A. Waggener. *Am. J. Physiol.* 85: 365-366. 1928.

Plummer, Kendall and others have suggested that the action of the thyroid hormone on the tissues of the body, with accompanying changes in metabolism, is probably catalytic in nature. The very marked delay in the action of thyroxin when injected intravenously into normal or myxedematous patients is hardly in accord with what we know regarding catalytic action. The same objection may be more strongly applied to an assumed drug-like action of thyroxin on the tissues. It occurred to us that this might not be a direct action of the hormone, but an indirect one, in which the intracellular oxi-

dizing systems are the immediate structures involved. To test this assumption experimentally, we have examined certain tissues (heart muscle, kidney cortex, liver and skeletal muscle) from three cretin lambs (twelve weeks after thyroidectomy) and three cretin pups (four and one-half months after thyroidectomy), together with similar tissues from normal animals of the same age and sex (twins and litter mates), for their power to catalyze the oxidation of a-naphthol and dimethyl-paraphenylene-diamine-hydrochloride into indophenol blue. Quantitative determinations were made by an improved colorimetric method. A marked diminution in the power of the tissues from thyroidectomized animals to catalyze the oxidation of the substrate was found in each case, with the exception of liver. Higher values were obtained for this tissue in two of the three lambs, while lower oxidation rates were found in all the tissues examined from the pups without exception. This diminution in amount, activity, potency or other property of the tissue oxidase of cretin lambs, as compared with that of the control animal taken as unity, averaged 15 per cent for heart, 45 per cent for kidney, 20 per cent for liver and 50 per cent for skeletal muscle in 20-minute readings. Lower values were obtained for the pups, in which the tissues were affected more equally; viz., heart, 16 per cent; kidney, 13 per cent; liver, 21 per cent, and skeletal muscle, 9 per cent. These figures compare favorably with the well known fact that basal metabolism may be reduced 30 to 40 per cent below normal in cases of hypothyroidism.—Authors' Abst.

Does the feeding of cod-liver oil prevent tetany in thyroparathyroidectomized dogs? Greenwald, I., *Am. J. Physiol.* 85: 376. 1928.

The feeding of cod-liver oil for two or three weeks before thyroparathyroidectomy, and thereafter, did not protect dogs against tetany. This is contrary to the results reported by Jones.

—Author's Abst.

The effect of ultraviolet light upon thyroparathyroidectomized rats. Jung, F. T., *Am. J. Physiol.* 85: 383. 1928.

Thyroparathyroidectomized male white rats, kept on a standard diet and weighed daily, were divided into two groups of equal average weight and were exposed daily to the light from mercury-vapor quartz lamps of known strength. The backs of the rats were shaved, and the dosage was approximately fifty times that necessary to produce an erythema in the unhabituated human subject. One group (controls) were shielded from the ultraviolet component of the light by being covered with glass plates. In the first experiment 26 rats were used, and irradiations were begun on the day of the operations. At the end of an arbitrary time limit the mortality,

severity of tetany, and loss in weight were studied; the results agreed in showing a favorable effect of the ultraviolet light. In a second experiment thirteen rats were used, and the irradiations were begun three days before operation. The results were again positive. The conclusions of Swingle and Rhingold from experiments on dogs are therefore corroborated.—Author's Abst.

Seasonal and geographic variations in the iodine and thyroxin content of the thyroid. Kendall, E. C., Proc. Assoc. Am. Physicians, May, 1928. Abst., J. A. M. A. 91: 121-122. 1928.

Kendall reports the analysis of 100 pounds of fresh hog thyroid glands during the first few days of each month for the past twenty months. In addition, various samples of thyroid material from different parts of the United States and England have been analyzed. It has already been shown by other workers that there is a seasonal variation in the total iodine. The author has confirmed this and found that in January and February 100 pounds of thyroid may contain 14 grams of iodine, while in July and August the iodine increases to about 40 grams, so that there is about 300% variation in the total iodine content. The amount of thyroxin in these glands has also been determined. The importance of considering the compounds which are not thyroxin and which contain iodine is shown by the fact that in the summer, when the iodine content is highest, the proportion of total iodine in the form of thyroxin is not more than 10%. This figure is for almost pure thyroxin (more than 90% thyroxin). In the winter there is a decrease in the amount of total iodine in the form of thyroxin and it may drop to less than 5%, so that from 90 to 95% of the total iodine in the gland is in some other form than thyroxin. The seasonal variation apparently does not occur in the English and Scottish glands. The amount of iodine apparently is uniform. The relationship between the iodine compounds of the thyroid does change greatly when the material is allowed to stand, so that it appears certain that some chemical change can occur in thyroxin when the glands are desiccated or when they have been freshly ground. This modifies the thyroxin in such a way that it is chemically altered and cannot be isolated, but it is still physiologically active. It appears certain that there is another iodine compound in the gland which has the same physiologic activity as thyroxin. This compound is unstable but it is found in the insoluble fraction. The fact that 10% of the total iodine is the maximal amount of thyroxin makes it impossible to account for the activity of desiccated or fresh thyroid by saying that it is all contained in thyroxin. The only conclusion that can be drawn is that some compound is present that is destroyed with alkali, is stable, at least to some degree, to acid, is not thyroxin, but has the physiologic ac-



tivity of thyroxin. Thyroxin appears to be an intermediate form of the active constituent. It must be altered before it can become physiologically active. After this alteration has occurred, it manifests the typical physiologic activity of desiccated thyroid, but it cannot be isolated. It is too unstable. Apparently allowing thyroid material to stand may alter the thyroxin content. This alteration does not consist merely in a detachment of the thyroxin from the protein. If that were so, then the thyroxin could be recovered. It must be some more deep-seated modification, and may possibly be the attachment of a second hydroxyl group to the thyroxin.

Observations on the antagonism between thyroid and thymus in controlling body weight (*Recherches sur l'antagonisme du thymus et du corps thyroïde au point de vue de leur influence sur le poids du corps*). Křiženecky, J., *Compt. rend. Soc. de biol.* 98: 1031-1033. 1928.

In pigeons fed with thyroid there is a marked reduction of body weight. With thymus the reduction is slight. If thymus and thyroid are fed together, the former antagonizes the effect of the thyroid and there is only a slight reduction.—J. C. D.

Concerning the influence of hyperthyroidism and hyperthymism on the maturation, growth and pigmentation of the feathers in full grown fowls (*Ueber den Einfluss der Hyperthyreoidismus und des Hyperthymismus auf Reifung, Wachstum und Pigmentierung des Gefieders bei ausgewachsenen Huhnern*). Křiženecky, J. and J. Podhradsky. *Arch. f. Entwicklungsmechn. d. Organ.* 112: 577-593. 1927.

Pure bred fowls of both sexes were fed thyroid and thymus separately and in combination. Hyperthyroidism hastened and stimulated moulting and feather growth, and produced depigmentation and partial albinism. These effects were uninfluenced by hyperthymism, nor did the latter produce effects of its own. The only sign of thyroid feeding that appeared in the moult following cessation of the latter was its incomplete patchy character. Partial albinism was transitory, occurring only while hyperthyroidism was maintained.—H. B. Torrey.

Further experiments on the influence of the thyroid and the thymus on feather development in poultry (*Weitere Versuche ueber den Einfluss der Schilddruese und der Thymus auf die Entwicklung des Gefieders bei den Huhnerrkuecken*). Křiženecky, J. and M. Nevalonnyj, *Arch. f. Entwicklungsmechn. d. Organ.* 112: 594-639. 1927.

Four races of pure bred fowls, that varied somewhat in their responses to thyroid, were used. In general it appeared that hy-

perthyroidism hastened the appearance of contour feathers; produced albinism that first affected the downy basal portions of the feathers resembling in this respect the feathers of the alpine crow (*C. cornix*) and, according to the authors, for the same reason; changed both structure and pigmentation of the feathers in both sexes toward the female type—the latter being regarded rather as a product of constitutional hyperthyroidism than the direct result of ovarian activity. Contrasted with these results were those associated with hyperthymism which, while not influencing the form and sexual characteristics of the feathers, inhibited somewhat the feathering out of the chicks and intensified the plumage pigmentation.—H. B. Torrey.

Experiments on the function of the thyroid and the thymus in the regeneration of plucked feathers (*Versuche ueber die Funktion der Threoidea und der Thymus bei Neubildung des ausgerupften Gefieders*). Křiženecky, J., M. Nevalonnyj and I. Petrov. *Arch. f. Entwicklungsmechn. d. Organ.* 112: 640-659. 1927.

Desiccated thyroid and thymus, separately and in combination, were fed to pigeons some of whose dorsal feathers had been plucked. Neither the rate of regeneration nor the form of the feathers replacing the old ones was affected. Hyperthyroidism stimulated moulting, hyperthymism to a less extent. In combination, hyperthyroidism plus hyperthymism produced a greater effect than the sum of their effects, separately.—H. B. Torrey.

The prevention of fatal parathyroid tetany in thyroparathyroidectomized dogs, by the administration of thyroid hormone. Kunde, M. M., R. Oslund and R. Kern. *Am. J. Physiol.* 85: 387. 1928.

Dogs in a hyperthyroid condition may be thyroparathyroidectomized and fed a diet containing 200 to 400 grams of meat daily without the occurrence of fatal parathyroid tetany, provided the hyperthyroid condition is maintained. The blood calcium and phosphorus are normal in these dogs, as is also renal function.

—Authors' Abst.

Influence of internal secretions and of trephones on phagocytosis. Morgulis, S. and B. A. Schatzillo. *Am. J. Physiol.* 85: 396. 1928.

Phagocytosis in normal serum as well as in serum of castrated or thyroidectomized animals is increased through the addition of trephones. The addition of trephones to thyroxin increases the phagocytosis of normal serum or of serum from thyroidectomized animals. The phagocytosis of serum from castrated animals is little altered from that of normal. Phagocytosis is diminished both after thyroidectomy or after parathyroidectomy. The phagocytic reaction in vivo of parathyroidectomized dogs is lowered. Tre-

phones exert no effect on the placental hormone, and the placental hormone has practically no influence on phagocytosis. Under the influence of trephones not only is the number of phagocytosing cells increased, but the quantity of material ingested is likewise markedly increased.—Authors' Abst.

**Basal metabolism. III. Influence of work with special reference to the thyroid gland.** Smith, J. H., Arch. Int. Med. 42: 47-52. 1928.

In fifty subjects the basal metabolic rate was determined, followed by a determination of the rate as influenced by imposing a load of one-twelfth the subject's body weight. All subjects with toxic goiter and with abnormally high basal rates (twelve) showed an increase in rate under the load varying from 22 to 64% of the subject's normal basal rate, and averaging 36.9%. The average of thirty-eight other cases was 14.1%. Two of the three subjects with toxic goiter and with basal rates under plus 20 who are taking compound solution of iodine showed a rise under the load suggestive of the thyroid hyperfunctional state; one did not show any rise above the normal of 20%. In three cases in which the basal rates were above plus 20 and in which there was no rise above 20%, none of the patients was found to have toxic goiter. Of the subjects with borderline basal rates not showing a rise of more than 20%, only the two patients taking compound solution of iodine were found to have toxic goiter. No fixed ratio appeared to exist between the increased basal rate of subjects with toxic thyroid and their abnormal response to work further than that the cost of work is higher than normal. An increased response to work did not appear to be a specific thyrotoxic phenomenon.—Author's Summary.

**The effect of thyroid therapy on children.** Topper, A. and P. Cohen, Am. J. Dis. Child. 35: 205. 1928.

The effect of thyroid therapy was studied in 14 children. In 4 patients with subnormal thyroid activity as evidenced by subnormal basal metabolism and clinical symptoms of hypothyroidism, thyroid in small or moderate doses promptly brought the basal metabolic rate to the normal level, where it remained even after the thyroid therapy was discontinued. In one child with a normal metabolism 12 grains of thyroid extract by mouth with 5 mgm. of thyroxin caused a transient increase in the pulse rate and basal metabolism. In 9 children with normal basal metabolic rates doses up to 15 grains daily did not increase the metabolic rate. A marked increase in growth was observed in 4 of these children. Since thyroid extract in relatively large doses does not seem to have any effect on the basal metabolic rate of normal children but has a stimulative effect on growth, one should question whether this rate should

be the criterion of the effects of thyroid therapy in normal children. The action of thyroid on normal children differs from that on normal adults. On this basis, the authors offer a theory to the effect that thyroid is a normal catalyst which increases the phase of metabolism dominant in the individual anabolic or growth processes in the child and katabolic or oxidative processes in the adult. Thyroid affects the growth processes of the normal child but has no effect on the basal metabolic rate, whereas in the adult where the growth processes are complete, the metabolic rate is changed.

—M. B. G.

**Iodine compounds.** Their selective absorption by the hyperplastic thyroid gland in the dog. Van Dyke, H. B., *Arch. Int. Med.* 41: 615. 1928.

An attempt was made by acute experiments to determine quantitatively the rates at which the hyperplastic thyroid gland of the dog selectively absorbs various iodine compounds. Thyroxine iodine was very slowly taken up, while free iodine was absorbed relatively more rapidly. Iodate iodine was bound quickly by such glands but apparently not so quickly as iodide iodine, which is selectively absorbed by the hyperplastic gland more rapidly than any of the iodine compounds studied. The selective absorption of iodine, iodate and iodide iodines was unaffected by complete bilateral ligation of the suprarenal glands six or seven hours previously.—Author's Abst.

**Ophthalmoplegia in Graves' disease.** Wedd, A. M. and H. H. Permar. *Am. J. M. Sc.* 175: 733-740. 1928.

A case of recurrent Graves' disease is reported in which the symptoms begin with visual disturbances due to external ophthalmoplegia, and death resulted during a thyroid crisis. The post-mortem examination revealed changes in the thyroid gland believed to represent an exhausted state. There were degenerative changes in the adrenal cortex, while the thymus showed an unusual degree of degeneration. The ophthalmoplegia in the case studied is believed to have been a part of the Graves' syndrome and not an expression of an independent symptom complex.—Authors' Summary.

**Proof that desiccated thyroid increases sugar utilization while commercially prepared thyroxin and other iodine compounds do not.** Wickwire, G. C., L. D. Seager and W. E. Burge. *Am. J. Physiol.* 85: 412. 1928.

One hundred milligrams of desiccated thyroid containing 0.55 mgm. of iodine were dissolved in 100 cc. of 0.1% dextrose solution. Similarly amounts of thyroxin, calcidine, potassium and sodium iodides containing the same amount of iodine as the 100

mgm. of desiccated thyroid were added to other 100 cc. portions of 0.1% dextrose in beakers. One portion of sugar solution to which nothing was added served for control. Two gold fish with a combined weight of approximately 5 grams were introduced into each beaker. Air was kept bubbling through the sugar solutions to insure an adequate supply of oxygen to the fish. Sugar determinations of the solutions were made immediately and after thirty hours according to the method of Benedict. None of the iodine compounds affected sugar utilization except the desiccated thyroid. This produced an increase of more than 50% over the control. Several experiments similar to the preceding were done with comparable results. Much larger quantities than the above of thyroxin, calcidine, potassium and sodium iodides were used and in no case was utilization increased above the control, while smaller quantities of desiccated thyroid gave a marked increase in sugar utilization.—Authors' Abst.



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